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SURGICAL MANAGEMENT OF VASCULAR DISEASE

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EUROSURGERY

Promoting Research and Training in Surgery

European Congress of Surgery

2–5 June 1992
Brussels

The Second European Congress of Surgery 'Eurosurgery 92' will take place in Brussels in June 1992. This meeting will pursue the aims of Eurochirurgie/Eurosurgery to promote research and training in surgery.

Preliminary Scientific Programme

I. General topics

2 June	What is new in European surgery? Computers in clinical surgery AIDS and surgery New aspects of laser surgery
3 June	Surgery in the aged
4 June	War/tropical surgery Ambulatory surgery History of surgery
5 June	Decision making in surgery Theoretical surgery Insurance implications in surgery Stapling in surgery Cost of surgical activity Organization of the operative complex Surgical nursing symposium

II. Abdominal and Oncological Surgery

2 June	Gastro-oesophageal reflux Gastric stump cancer Colon cancer Hydatid cyst of the liver Motility disorders of oesophagus
3 June	Saving the spleen Diverticulitis of the colon Colonic volvulus Laparoscopic cholecystectomy symposium Prospects and future of laparoscopic surgery Colon carcinogenesis
4 June	Abdominal surgery by laparoscopy Laparoscopic surgery training Cancer of the oesophagus Oesophageal diseases Reducing sepsis in colorectal surgery Infections in abdominal surgery Liver metastases Hirschsprung's disease Major hepatic surgery
5 June	Acute pancreatitis Radical surgery in rectal cancer Adjuvant treatment in rectal cancer Stoma therapy Stapling in surgery

III. Training in Surgery

2 June	Specialisation in general surgery
3 June	Training in surgery Surgical training in Eastern Europe
4 June	Laparoscopic surgical training Surgical video session

IV. Transplantation Surgery

5 June	Multiorgan harvesting and preservation in Europe Transplantation in Belgium Immunosuppression regimens Liver transplantation. new prospects

V. Traumatology and Orthopaedic Surgery

3 June	Saving the spleen
4 June	Early management of multiple trauma Arthroscopic surgery in 1992 Hand surgery Treatment of major pelvic trauma

VI. Paediatric Surgery

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VII. Thoracic and Oncological Surgery

2 June	Early breast cancer Gastro-oesophageal reflux Oesophageal motility disorders
3 June	Advanced breast cancer
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5 June	Stapling in surgery

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5 June	Diagnosis and multimodal therapy of thyroid cancer

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X. Plastic Surgery

4 June	Burn injury Microsurgery Hand surgery Malignant tumours of the face

XI. Gynaecological Surgery

3 June	Gynaecological laparoscopy

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The Danish Surgical Society

The Danish Surgical Society was founded on 28 October 1908 on the initiative of T. Rovsing (1862–1927) and E. A Tscherning (1851–1919), Professors of Surgery at the University of Copenhagen.

As laid down in its original statutes, the object of the Society was the advancement of Danish surgery through scientific cooperation among Danish surgeons. The object is to work for scientific cooperation among the members of the Society and among the societies of surgical specialties, and also to work for training and research within the field of surgery.

Today the Danish Surgical Society has over 750 members. A number of societies of surgical specialties are associate members, they are. the Danish Gastroenterological Society, the Danish Society of Thoracic Surgery, the Danish Society of Vascular Surgeons, the Danish Urological Society and the Danish Society of Plastic and Reconstruction Surgery.

The activities of the Society cover several fields; regular scientific meetings create a forum for the presentation of the members' scientific work. These scientific meetings may be in the nature of topic sessions, where works on a specific surgical topic are presented, or they may be meetings open for free presentations. During recent years the Society has arranged a more comprehensive annual meeting with the participation of lecturers from other countries and a programme of ten to 12 scientific sessions. The annual meeting could thus be characterized as a meeting for postgraduate follow-up training. Furthermore, the Society is responsible for the postgraduate training of surgical residents, partly by establishing continuous courses for doctors in the process of specialist training. These courses are compulsory, approved and subsidized by the Danish Ministry of the Interior. In addition, a number of postgraduate specialist courses at a more advanced level are arranged every year Such courses are voluntary, intended mainly for established specialists. The courses mentioned combined with the scientific meetings of the Society are today regarded as an essential part of the postgraduate training of Danish surgeons

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Asociacion Española de Cirujanos

The Spanish Association of Surgeons was officially founded in 1934 There are currently 1700 members; the Association is owner of the journal *Cirugia Española*, published monthly since 1950. Its main scientific activity is organizing the National Congress of Surgery, which takes place during November in Madrid. In these Congresses, the following societies participate conjointly: International College of Surgeons; International Society for Diseases of the Oesophagus; Collegium Internationale Chirurgie Digestivae; Spanish Association of Oncologic Surgery; Spanish Association of Breast Diseases; Spanish Association of Paediatric Surgery; Spanish Association of Transplants, and Spanish Association of Head and Neck Surgeons.

The participation of the Spanish Association of Surgeons within Europe is as a member of: International Society of Surgery; International Federation of Surgical Colleges, International College of Surgeons; Eurochirurgie; UEMS, and Surgical Infection Society.

In the last years, there have been created national committees for the study of specific surgical diseases, but maintaining the basic and unitary concept of general surgery: Surgical Infections; Hepato-Pancreato-Biliary Surgery; Surgical Research; Colorectal Surgery; Thoracic Surgery; Endoscopic Surgery; Viscerosynthesis, and Endocrine Surgery.

José L. Balibrea
President

Officers of the Association·
President: Professor José L. Balibrea
General Secretary: Professor Jesús M. Gonzales-Lobo

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Small bowel transplantation

Over 30 years ago Richard Lillehei and colleagues from Minneapolis carried out experiments demonstrating that, from a technical point of view, transplantation of the gut was feasible[1]. However, it rapidly became clear that compared with other forms of organ grafting there were major difficulties in achieving successful allogeneic small bowel transplantation. The small bowel has a substantial lymphoid component in the mesenteric lymph nodes, Peyer's patches and lamina propria. Therefore, in addition to recipient cells invading the graft to cause rejection, graft cells are capable of migrating to recipient tissues to cause graft *versus* host disease (GVHD). Controlling these competing immunological forces presents a considerable problem. Early clinical attempts at small bowel transplantation were all carried out in desperate cases where the patient had no other hope of survival. Although some patients lived for a few weeks, most succumbed within days of the procedure. It is now clear that systemic sepsis was the cause of death in these cases. Recent studies on immunocompromised patients receiving chemotherapy have demonstrated that in this situation bacteria can translocate across the bowel wall into the bloodstream and cause life-threatening infection. In transplanted bowel the effects of ischaemic injury following organ harvesting, combined with damage induced by early rejection, may compromise the mucosal barrier, with the rapid development of septicaemia.

In the 1980s the advent of cyclosporin, with its specific effect on T lymphocytes, rekindled interest in the possibility of small bowel transplantation. In experimental animal models cyclosporin was capable of completely subverting the rejection response. One of the fascinating observations has been that in long-surviving grafts the majority of the lymphoid tissue of the bowel is replaced by host cells[2]. Recent evidence indicates that a similar repopulation with recipient cells also occurs after human small bowel transplantation[3]. In other organ grafts such cellular infiltration is associated with rejection, but in a small bowel transplant the invading host lymphocytes clearly have a symbiotic relationship with the graft.

The development of potent new immunosuppressive agents bringing the possibility of successful human small bowel transplantation begs the question of whether there is a real clinical need for the procedure. From studies of patients currently on long-term total parenteral nutrition (TPN) it would appear that there are between two and three patients per million of population per year who develop irreversible small bowel failure[4]. These patients are children and adults who have had massive small bowel resection for conditions such as volvulus, enterocolitis, Crohn's disease, radiation enteritis and mesenteric vascular disease. If successful programmes could be established there would also be the possibility of offering treatment of infants with congenital problems, such as microvillus atrophy, which at the present time are uniformly fatal.

A number of isolated small bowel transplants were performed in Paris and Keil, Germany in the late 1980s, and two patients still retain functioning grafts more than 2 years after operation. In 1989 Grant and colleagues in London, Ontario performed a combined liver and small bowel graft with long-term success[5] and have now carried out two further procedures of this kind. At the Second International Symposium on Small Bowel Transplantation held in Canada in October 1991, Starzl reported successful results from Pittsburgh, USA, where there is now an eight-case series of liver plus small bowel grafts immunosuppressed with FK506. Although the mechanism remains obscure, it is known from animal models that a liver graft has a protective effect and can enhance the survival of other organ grafts[6].

Those patients surviving with small bowel transplants have all had stormy postoperative courses with lengthy periods in intensive care. Although transplantation is now a possibility for patients with intestinal failure there are still a number of important problems to solve. Only short-term preservation of the bowel is available at present, limiting the possibility of achieving good immunological matching of donor and recipient in cadaveric grafting. Despite the potency of the newer immunosuppressive agents, GVHD remains a potential problem which they may not adequately control. In the first liver plus small bowel case of Grant *et al.* there was documented evidence of GVHD[5] and this process appears to have been responsible

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for the one death in the Pittsburgh series. Experimental work using graft perfusion with monoclonal antibody–toxin conjugates directed against lymphocytes indicates that it is possible partially to deplete the lymphoid population before transplantation and so reduce the chance of GVHD[7]. This would be feasible in clinical transplantation and more acceptable than the alternative strategy of irradiating the mesenteric lymph nodes. Maintaining the integrity of the mucosal barrier remains a major concern and it is also important to determine whether a small bowel graft repopulated with host cells will be able to retain an adequate immune response to luminal antigens. Molecular biology techniques are enabling the precise intracellular pathways involved in immunosuppression to be determined. Combined with our knowledge of the structure of the T cell receptor there is a prospect of developing precisely targeted agents which will enable the competing immunological forces in small bowel transplantation to be controlled. The field is moving very rapidly and within the next 5 years small bowel transplantation will be a realistic alternative for patients currently maintained on home TPN.

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Digest

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For the past 18 months we have been carrying the list of contents of the previous month's issue of The American Journal of Surgery, *and that journal has carried our list of contents. In an attempt to increase awareness of each other's surgical literature, we are introducing a new venture in which we will exchange 'digests' on a quarterly basis. Below we publish the first such digest of* The American Journal of Surgery *prepared by Dr Hiram Polk, and that journal will carry a reciprocal digest of the last quarter's* British Journal of Surgery *prepared by our Editor, Professor John Farndon. Next month we will repeat the exercise with the German journal* Der Chirurg. *Comments specific to the content of individual papers in the digests should be addressed primarily to the source journal, but we would be glad to receive a copy.*

Pancreatic surgery

Surgeons' fascination with and respect for the pancreas continues Thompson, Rikkers and associates studied 90 patients with pseudocyst formation to see if pathogenesis was related to outcome[1]. Multiple pseudocysts were more frequent in acute than chronic pancreatitis Spontaneous resolution within 8 weeks occurred in 11 per cent of cases, but no pseudocyst of biliary or postoperative aetiology did so. Outcome did not correlate with size (±6 cm) or acuity of presentation Death occurred more often in patients with postoperative pseudocysts.

An endoscopic retrograde cholangiopancreatography (ERCP)-based algorithm as a means to allocate pseudocyst therapy based on findings of pancreatic duct obstruction or pseudocyst communication was assessed in a series of patients with pancreatic pseudocysts seen from 1984 to 1990[2]. Of 102 patients, 73 had symptomatic pseudocysts requiring treatment. Forty of the 69 elective interventions were preceded by ERCP and retrospectively applied to the algorithm. The number of adverse outcomes (treatment failures and complications) of the group that followed the algorithm was 3 of 26 (12 per cent). The number of adverse outcomes of the group that did not follow the algorithm was six of 14 (43 per cent) ($P < 0{\cdot}04$, Fisher's exact test) The two subgroups were similar in all other characteristics examined.

The summary of the Pancreas Club meeting in May 1991 by Dr Charles F. Frey is one of *The Journal*'s annual highlights[3]. This concise look at clinical and investigative aspects of the pancreas included reports from all North America's leading pancreatic clinics and laboratories.

Cardiac surgery

Cardiovascular topics continue to concern the rank and file practising surgeon. Guirguis and Barber reassessed the risk of rupture of 300 consecutive abdominal aortic aneurysms[4]. The mean age of the patients was 70·4 years, and 211 (70 per cent) were men. The mean initial aneurysm diameter was 4·1 cm. Among the 208 patients who underwent more than one ultrasonographic or computed tomographic scan, the diameter of the aneurysm increased by a median of 0·3 cm per year. The 6-year cumulative incidence of rupture was 1 per cent among patients with aneurysms less than 4·0 cm and 2 per cent for aneurysms 4·0–4·9 cm in diameter ($P > 0{\cdot}05$). In comparison, the 6-year cumulative incidence of rupture was 20 per cent among patients with aneurysms greater than 5·0 cm in diameter ($P < 0{\cdot}004$). They concluded that: (1) abdominal aortic aneurysms expand at a median rate of 0·3 cm per year; and (2) the risk of rupture of abdominal aortic aneurysms less than 5·0 cm in diameter is substantially lower than the risk of rupture of aneurysms 5·0 cm or more in diameter.

Cardiac contusion is largely monitored and treated by general surgeons with a constant thought for the optimal treatment of expensive heavily monitored patients. Illig *et al.* reviewed 133 patients with suspected cardiac contusion from two separate hospitals to determine whether death or morbidity would have occurred if all patients with normal electrocardiograms (ECGs) in the emergency department had been discharged (or admitted to unmonitored beds for other injuries)[5]. Only 13 patients developed cardiac problems, two elderly patients died in the emergency department, while others experienced arrhythmias or, less commonly, pump failure requiring treatment or observation. All 13 had ECG changes present while undergoing evaluation in the emergency department; 11 had a specific problem on arrival, one developed a problem while still being evaluated, and the 13th had what was probably an iatrogenic problem. Importantly, five of 12 patients had normal creatinine phosphokinase-MB fractions, and five of nine had normal echocardiograms. No patient with a normal ECG had subsequent cardiac problems. Operative intervention for other injuries was necessary in 26 patients overall, and there was no cardiac morbidity. Had the ECG been used as the sole screening tool, approximately 25 per cent of these patients could have been discharged from the emergency department without missing problems. Management would have been simplified and the hospital would have realized substantial savings both in terms of direct costs and freeing valuable and scarce resources.

Sepsis

Infection is an age-old problem for all surgeons and a variety of fresh insights have appeared recently. With the advent of ever more expensive putative therapies for infection, the confirmation of the diagnosis of bacteraemia is of greater importance. The effectiveness of venous blood cultures in febrile perioperative patients was studied by Theuer, Bongard and Klein[6]. Results of 364 blood culture vials representing 108 consecutive febrile events (temperature greater than or equal to 38·6°C) in 72 patients on adult surgical services without overt evidence of sepsis in a metropolitan hospital were studied prospectively. Eighty-nine per cent of patients had undergone an operation before the febrile episode. Micro-organisms were isolated in blood culture vials from nine of 108 patient febrile events Of these, five were positive (contained pathogens) and four represented contaminants. Two of the positive blood cultures occurred in patients with an identifiable source of bacteraemia. The cost of processing all blood culture vials was US $13 992 (£7500), which amounted to US $2798 (£1500) spent to identify each of the five patients with positive blood cultures. Blood culture vials were more likely to be positive if blood was drawn during days 4 to 10 after operation, as opposed to days 1 to 3, or if it was drawn from patients with depressed immune function or who had indwelling foreign bodies. Neither the magnitude of the absolute leucocyte count nor the maximum temperature at the time of phlebotomy predicted a positive blood culture. In no case did a positive blood culture have a measurable effect on reducing patient morbidity or mortality.

Direct application of antibiotics at or near the site of infection has also experienced a resurgence of interest. Ablan *et al* studied experimental peritonitis in 56 rabbits with treatment begun 2 h after peritoneal soiling[7]. The administration of no treatment resulted in a 100 per cent mortality rate. Parenteral cefotetan 25 mg/kg intramuscularly twice a day with no other treatment reduced the mortality rate to

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50 per cent ($P < 0{\cdot}05$). Cefotetan 25 mg/kg intramuscularly twice daily plus irrigation of the peritoneum with plain saline further reduced the mortality rate to 21 per cent. Cefotetan at the same dose plus irrigation of the peritoneum with saline containing cefotetan 1·0 mg/ml reduced the mortality rate to 14 per cent. These treatments also produced a progressive decrease in the mean(s.e.m.) number of intraperitoneal abscesses from 24·0(2·1) in the animals receiving no treatment to 9·7(1·2) abscesses in those receiving peritoneal irrigation with saline containing cefotetan ($P < 0{\cdot}001$) A second experiment was performed to examine the efficacy of intraperitoneal antibiotics A lethal faecal inoculum was determined in rabbits receiving parenteral cefotetan and irrigation of the peritoneum with plain saline. With 2 h delay before treatment, cefotetan 25 mg/kg and irrigation with plain saline produced an 80 per cent mortality rate Parenteral cefotetan plus cefotetan 1·0 mg/ml in the saline washout reduced the mortality rate to 21 per cent ($P = 0{\cdot}003$) and markedly reduced the number of intraperitoneal abscesses from 13·4(0·7) in the animals receiving irrigation with plain saline to 8·1(0·8) in those receiving irrigation with saline containing cefotetan ($P < 0{\cdot}0001$). They conclude that intraperitoneal antibiotics should be considered in all cases of peritonitis.

A related clinical trial was reported by Rosen *et al*[8]. They postulate that systemically administered antibiotic prophylaxis does not reach sufficiently high concentrations of antibiotic in the tissue of the sacroperineal wound. Since gentamicin-polymethylmethacrylate (PMMA) in the form of chains of beads has been confirmed as a useful tool in the treatment of local infection in bone and soft tissue surgery, they evaluated its effect on abdominoperineal excision in a prospective, randomized trial. Forty-four patients with rectal or anal carcinoma entered the study. The patients were treated with local gentamicin and drainage (group 1) or drainage alone (group 2), using the Lloyd–Davies procedure. The two groups were comparable regarding age, sex, tumour stage and level, and risk factors predisposing for an infectious complication (anaemia, nutritional status, blood transfusion) No patient died. Analysis of local perineal wound healing revealed a significantly higher percentage of primary wound healing in group 1 than group 2 (87 *versus* 46 per cent, $P < 0{\cdot}01$). This led to a significantly shorter hospitalization period for patients in group 1 ($P < 0{\cdot}01$). Gentamicin-PMMA chains exerted a favourable effect on local wound healing and the postoperative outcome of patients with abdominoperineal rectum excision.

Laparoscopy

Less invasive forms of surgical care grew in popularity and scientific interest. Schirmer *et al.* found that the rate of laparoscopy increased 117 per cent, with residents performing as surgeon in 59 per cent and as surgeon or first assistant in 86 per cent of therapeutic laparoscopies[9]. Complication rates were 0·03 per cent in 1989 and 0·2 per cent in 1990 for diagnostic laparoscopy but 4 per cent for therapeutic laparoscopy. There was no difference in complications whether the resident was or was not acting as surgeon Goodman and Hunter described a favourable experience with the first 100 laparoscopic cholecystectomies in a university teaching hospital[10] Two procedures were converted to 'open' operations and a bile duct was injured. Ninety-seven patients were discharged in less than 24 h and real cost savings were noted. Hunter separately described transcystic common bile duct exploration (CBDE) for unsuspected stones found during laparoscopic cholecystectomy by a single surgeon in 150 consecutive patients[11]. If the cholangiogram appeared to show common bile duct (CBD) stones, a 5 Fr 8-mm ureteral stone basket was passed through the cystic duct into the duodenum, opened, and trolled through the CBD. Routine cholangiography was successful in 131 of 144 attempts (91 per cent). An indication for CBDE was found by cholangiogram in seven patients (5 per cent) Two cholangiograms were falsely positive. Stones were removed in five patients. Completion cholangiograms were normal in all patients. One patient developed mild pancreatitis but was discharged 2 days after laparoscopic cholecystectomy. The remainder were discharged on day 1 after operation. One patient was readmitted possibly having passed a retained stone. Fluoroscopic CBDE was successful in clearing the CBD in all patients in this small series.

Colorectal surgery

Buess *et al.* described a further experience with transanal endoscopic surgery for early rectal cancer[12]. They developed a new minimally invasive technique for tumour resection A rectoscope with 40 mm diameter enabled tumour resection under stereoscopic control in the gas-dilated rectal cavity. Excisions in full-thickness technique up to segmental resections with an end-to-end anastomosis were conducted. Most local resections of carcinomas were performed when removal of an adenoma was planned and the postoperative histology showed a carcinoma Since 1983 326 patients were operated on and 274 were documented in a clinical trial, 74 having carcinomas. The rate of severe complications in patients with carcinomas was 9 per cent, the mortality rate was zero. The stereoscopic magnified view in the gas-dilated rectum allows precise surgery in this operative field that is otherwise difficult to reach. In the postoperative course minimal discomfort and pain result in a short hospitalization period.

As the Society for Surgery of the Alimentary Tract State-of-the-Art address, Kelly further described the remarkable Mayo experience with sphincter-preserving operations for ulcerative colitis[13] The ileoanal pouch has proved safe and permits continence and satisfactory defaecation and function in the vast majority of such patients. This experience has changed the goals and priorities in the treatment of this debilitating chronic illness and eliminates the ultimate risk of cancer as well

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Anal fistula

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Anal fistula is a common cause of chronic irritation to both patients and surgeons. Treatment failure rates may be decreased by a good appreciation of normal anorectal anatomy and fistula pathoanatomy, as well as a wide and practical knowledge of the possible treatment regimens. The various treatment options available for acute abscesses as well as simple and complex anal fistulae are presented and discussed. Identification of the patient at risk of postoperative anal incontinence or of the difficult or high fistula may allow treatment in a specialized proctology unit.

Although recognized as a distinct entity for hundreds of years, anal fistula continues to be a difficult surgical problem. Hippocrates, writing in the fifth century BC, argued for the laying open of an anal fistula, stressing that those who are left without treatment die[1]. John of Ardene in 1376 said that the treatment of anal fistula had fallen into disrepute because it was a troublesome condition which brought very little credit to surgeons and required long and patient treatment He advised his students not to do too much at one sitting in complex fistulae[2–4]. Lowe in 1612 wrote that it was better not to operate on the very complicated fistula owing to the danger of producing incontinence[5] Having been asked to treat King Louis XIV, Felix, the 18th century Parisian surgeon, rediscovered anal fistulotomy after experimenting on the inmates of Parisian jails The cured and extremely grateful king granted Felix an honorarium, an estate and a title, and thereby greatly elevated the craft of surgery[6]. It was partly the notoriety of anal fistula that led Salmon to found St. Mark's Hospital in 1835 for the relief of the poor in London afflicted with fistula and other diseases of the rectum[7]. Lockhart-Mummery noted in 1929 that probably more reputations had been damaged by the unsuccessful treatment of cases of fistula than by excision of the rectum[8].

Since then, although much has been written about anal fistula, a great deal remains uncertain and controversial and the ailment continues to be troublesome to both surgeons and patients. This review deals with some of these issues and is limited to idiopathic or non-specific anal fistula and abscess. Specific causes of anorectal sepsis which will not be reviewed include Crohn's disease[9–11], tuberculosis[12], actinomycosis, various malignancies[13–19], gut duplication[20], foreign bodies[21] as well as intra-abdominal or pelvic disease[22–24]. Rectovaginal and urethrorectal fistulae are not discussed.

Epidemiology of anal fistula

The majority of studies on anal fistula involve small groups of selected patients. Men predominate in most series with a male:female ratio varying from 2:1 to 7:1[25–28]. Age distribution is spread throughout adult life with the maximal incidence between the third and fifth decades[25–29]. Sainio[29] examined anal fistula in a defined population of 510 000 over a 10-year period and found the incidence for men to be 12·3 per 100 000 and that for women 5·6 per 100 000.

Pathogenesis of anal fistula

The cryptoglandular hypothesis for the pathogenesis of anal fistula postulates that anal glandular infection is the primary cause of fistula and abscess[8,25,30–33]. Our understanding of anal glands is sketchy and nothing is known about their function in humans. Chiari[34] (1878) followed by Herrmann and Desfossess[35] (1880) were probably the first workers to point out the relationship between anal intramuscular glands and anal fistula. Herrmann (1880), however, did not find any trace of secretory epithelium in these glands and preferred to call them intramuscular sinuses[36]. Braun (1901) was not able even to prove the presence of these glands and completely denied their existence[37], Johnson (1914) being the first to describe their detailed anatomy[38]. He stated that two types of anal gland arise from the lower part of the rectal sinuses The first is a simple tubular structure which lies completely within the submucosa. The second type consists of branched tubules which pierce the muscular layers and are called intramuscular glands. There are seldom more than six or eight of the latter in each anorectum He showed that the main glandular duct usually extends downwards and outwards to penetrate the internal sphincter From the ampulla-like swelling of the duct at this point, several smaller tubules then branch out through the internal sphincter to end blindly in the intramuscular connective tissue. Rarely one of these tubules may be observed to pierce the longitudinal muscle layer. Johnson further noted that the terminal portions of these tubules are surrounded by a small amount of lymphoid tissue and that these cells are secretory in the fetus and at birth. Bremer noted that secretory cells disappear from the anal gland epithelium soon after birth[39]

Lockhart-Mummery postulated that these glands afford a path for infecting organisms from the bowel to cause perirectal abscesses[8]. Tucker and Hellwig showed that it was infection of these anal glands rather than cryptitis that causes perianal infection[40–42]. Gordon-Watson and Dodd illustrated this point when they reported three cases of anal fistula lined in part with anal glandular epithelium[43]. Nevertheless Fowler found only three of 20 specimens in which the anal glands had penetrated the internal sphincter, and concluded that the continued use of the term intramuscular glands was likely to sustain widespread misconception as to their site and function; anecdotal observations had already been overused in attempts to explain the spread of anorectal suppuration[44] Parks and others, however, argued that anal fistula was caused by infected anal glands in the vast majority of cases and suggested cystic dilatation of the anal glands as a necessary precursor to infection[8,45–47]. However, Parks did not find any evidence that these glands penetrate the external sphincter[30]. Although rare, with an incidence of 0·05 per cent, perianal cysts lined by anal gland epithelium have been reported[48] Morgan and Thompson[49] and Shropshear[50] postulated that infection spreads from the anal canal into the perianorectal tissue to form fistulae and abscesses by tracking along the fibres of the longitudinal anal muscle which pass inwards through the internal sphincter as well as outwards through the external anal

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sphincter muscle. Hiller thought that micro-organisms first penetrate the submucosal space and then track along the perivascular spaces to reach the poorly nourished fatty perirectal areas where abscesses and fistulae form[51].

Other workers have stressed the wide individual variation in the number, depth and shape of the anal glands, postulating that this explains the individual susceptibility to anorectal sepsis[52,53]. Kratzer and Dockerty showed that anal ducts are found in about 50 per cent of anal canals of which 33 per cent penetrate the internal sphincter, and that mucus-producing cells may be demonstrated in 10 per cent of duct linings[54]. They also concurred with other studies showing that most of the ducts had their orifices in the posterior portion of the anal canal[55,56], postulating that this is the explanation for the predominance of posterior anal fistulae[54]. Burke *et al.*[57] stated that the site of occurrence of anal ducts is usually around 12 o'clock posteriorly (presumably 6 o'clock in the lithotomy position). Parks disagreed with earlier investigators by reporting that anal glands are distributed equally around the circumference of the anal canal[30]. Anal glandular secretion, although scanty, has been investigated histochemically, but its function, if any, is still unknown[58]. Goligher questioned whether anal glands have any secretory function at all[59]

Most workers have reported that anal glands open into the lower end of the anal crypts but that the occasional duct may open at a slightly higher level[60]. It is not uncommon to find two to four anal glands per crypt[56]. McColl found anal glands in all anal canals examined although only 50 per cent were intramuscular and 60 per cent were mucus-secreting; he postulated that these two characteristics predispose patients to anal fistulae[61]. Lilius, however, concluded his academic dissertation by stating that anal intramuscular glands are not found in all individuals and not everyone, therefore, can develop a fistula of anal intramuscular gland origin[62]. He also noted that men have a slightly higher incidence of anal intramuscular glands than women.

Goligher *et al.* demonstrated intersphincteric abscesses in only eight of 28 cases with anorectal suppuration or fistula and concluded that, although cryptoglandular infection may lead to a proportion of anorectal abscesses and fistulae, it cannot be used to explain the causation of the great majority[63]. Furthermore, chronic anal fistulae do not seem to be maintained by specially virulent organisms[64]. Shafik has renewed the controversy by suggesting that anal intramuscular glands are developmental vestiges rather than true glands and that it is sequestrated epithelial debris from the developing anorectal sinus that perpetuates subsequent infection[65]. This has been challenged in a recent paper describing histological examination of 62 autopsy specimens which failed to reveal evidence of epithelial debris in the subanoderm[66]. Shafik also postulated that anorectal sepsis and fistula results from an initial infection in the central space, which is a circumferential space in the lower perianal region bounded superiorly by the termination of the longitudinal muscle and inferiorly by the lowermost loop of external sphincter[67,68]. The longitudinal anal muscle ends at the superior border of the central space to continue as the central tendon within the central space The central tendon then decussates to insert into the perianal skin as the corrugator cutis ani[67]. Infection spreads along the septa of the central tendon from the central space into the perianal and perirectal spaces[49,50,65,67,68] The question of the relationship of anal glands to anal fistula is thus far from settled

Classification of anal fistula

Accurate and meaningful descriptions of complex fistulae can be difficult. A system of classification should provide accurate and easily understood information that will permit wide understanding of what is being described and enable therapeutic options to be compared. Many systems of classification have been used throughout the world; most are complex and impractical for routine clinical usage. Only the more important ones will be discussed.

In 1900 Goodsall and Miles commented that the three forms of fistula recognized by all surgeons are the complete, the blind external and the blind internal, with the last further subdivided into subcutaneous, submuscular and submucous[69,70]. Following advances in the knowledge of surgical anatomy, Milligan and Morgan were able to refine this classification. They retained the subcutaneous and submucous fistulae and divided the more complex fistulae according to their relationship to the anorectal ring[71–73]. Tracks were divided into low anal with the main track below the anorectal ring, high anal with the main track below the anorectal ring, and anorectal with the track extending above the anorectal ring. The last group was further subdivided into those with an internal opening into the rectum, those without an internal opening, and those that open into the anal canal below the anorectal ring. The site of the internal opening is the most vital consideration in this classification. If this is below the anorectal ring, the fistula can always be laid open without fear of major incontinence. If the anorectal ring is divided incontinence will inevitably result[71]. Although gross faecal incontinence can be prevented by preserving the puborectalis, anal function after operation may be compromised by division of the internal and external anal sphincters[74]. Eisenhammer clarified the anatomy of the high submucous fistulous abscess and clearly demonstrated that it was actually within the intermuscular plane, i.e. between the circular and longitudinal internal anal muscles[75,76]. Goligher further subdivided high anorectal fistulae into the ischiorectal type, in which tracks extend only as far as the top of the ischiorectal fossa, and the pelvirectal type in which tracks penetrate the levator ani to end blindly in the supralevator tissues[77]. These two types are known also as infralevator and supralevator extensions respectively[59]. Steltzner identified three groups: the intersphincteric fistula where the fistula lies between the internal and external sphincter muscles, the trans-sphincteric where the fistula crosses the external sphincter to enter the ischiorectal fossa, and the extrasphincteric where the fistula passes from the rectum through the levator ani outside of the external sphincter to the skin[78].

Parks *et al.*[79] built on this classification by relating their system to both the cryptoglandular origin of the fistula and to the anal sphincters and levator ani. Superficial fistulae were not included in their classification as they were considered to be of different aetiological origin. They divided anal fistulae into four major groups. Intersphincteric fistulae were subdivided further into: simple; with high blind track; with high track opening into the rectum; without a perineal opening; with pelvic extension, and those due to pelvic disease. Trans-sphincteric fistulae have tracks that may penetrate the external sphincter at varying levels, i.e. high or low, and could be subdivided into uncomplicated and those with a high blind track. Suprasphincteric fistulae pass upwards in the intersphincteric plane to loop over the top of the puborectalis and emerge through the levator ani to reach the skin. The fourth group consists of the extrasphincteric fistulae. Fistulae are classified according to the course taken by the main or primary track, which is the track linking the internal and external openings. Secondary tracks are defined by qualifying the primary tracks, e.g. trans-sphincteric track with a supralevator extension. The term 'secondary tracks' or 'extensions' is usually used for important extensions from the main or primary track. An important type of secondary track is that due to circumferential spread or horseshoeing; it takes place mainly in the intersphincteric, ischiorectal or supralevator planes[79]

Thompson divided fistulae into simple or complex depending on the relationship of the track to the puborectalis[80]. A complex fistula is one with a high track that extends above the puborectalis while a simple fistula does not. Eisenhammer divided primary acute cryptoglandular fistulous abscesses into three groups: low intermuscular; high intermuscular; and intermuscular–trans-sphincteric ischiorectal abscess–fistula.

He maintained that suprasphincteric and extrasphincteric fistulae are of iatrogenic and not cryptoglandular origin[81,82]. Shafik disagreed with the cryptoglandular hypothesis for the genesis of anal fistulae and has classified fistulae in relation to the central space and the external anal sphincter. He divided anal fistulae into intrasphincteric and extrasphincteric[68]. An intrasphincteric fistula starts as a central space infection which may then track up the intersphincteric spaces or out to the skin but is always medial to the external sphincter. An extrasphincteric fistula also starts as a central space infection but tracks lateral to the external anal sphincter.

The most widely used system is probably that of Parks *et al.*[25,79] and subsequent discussion will be based on this system.

Evaluation of anal fistula

Accurate preoperative delineation of the anatomy of an anal fistula is important if recurrence or incontinence after operation are to be avoided[83]. The five essential points to be obtained from a clinical examination of an anal fistula were enumerated as long ago as 1900[69]. These are the location of the internal opening, the external opening, the primary track and the secondary track, and the presence or absence of underlying disease. The external opening is usually obvious so that the pathoanatomy of most fistulae can be delineated clinically by locating the internal orifice and defining the presence and type of secondary extension[84]. Digital examination has been shown to be up to 79, 84 and 71 per cent accurate in defining the internal opening, primary track and secondary track of anal fistulae respectively[85]. Poor resting tone before operation or voluntary anal contraction respectively indicate an already compromised internal or external anal sphincter function, and mean that conservative surgery may be necessary to avoid anal incontinence[86].

Systematic and careful examination is important and will give the clinician useful data about the pathoanatomy of the fistula[87]. Intersphincteric tracks tend to open externally close to the anal verge while trans-sphincteric and more complicated fistulae will tend to open further away[88]. The major problem is in locating the internal opening Edwards[89] was the first to point out what has now come to be known as Goodsall's rule[69]. He stated in 1887 that fistulae which have their external opening behind a plane passing transversely through the centre of the anus usually have their internal aperture in the midline posteriorly, while those with an external orifice anterior to this plane have their internal opening immediately opposite[89]; 61–69 per cent of internal openings are located in the posterior quadrant of the anal canal at the level of the dentate line[26–28,62,90].

Internal openings may be felt as indurated nodules or pits leading to an indurated track[90] or they may be seen to exude pus when the tracks or abscesses are gently massaged[91] Fibrosis is a frequent pointer to the site[90]. Gentle use of probes along the dentate line or through the external opening may be useful in locating internal openings[90]. Besides the use of probes, intraoperative injection of methylene blue, saline or other solutions has been advocated[92–94]. Methylene blue is perhaps the most widely used but it is not particularly helpful; its use has been compared to pouring ink on to a newspaper to facilitate reading[84,95]. The injection of 0·5–2 ml hydrogen peroxide through the track may help locate the internal orifice by producing a stream of white bubbles at the latter site[96] Larger amounts of undiluted 3 per cent solution should not be used in closed cavities because systemic absorption may lead to gas embolism and death[97,98]. If the internal opening cannot be found but the probe tip is in the immediate vicinity of the dentate line, a direct association may be presumed[99]. When the internal opening cannot be found and the probe tip is remote from the dentate line, it is probably safer to leave the search to another day[99]. Intraoperative traction on the external opening or track may sometimes show a dimple at the site of the internal opening[100] Granulation tissue that will not curette away is a helpful marker and guide to the presence of secondary tracks[84,101].

Fistulography is unreliable, it is correct in only 16 per cent of cases and might be harmful since it has been associated with a 12 per cent incidence of false rectal openings and high extensions, which could lead to unnecessary and harmful exploration[102]. Nevertheless, a recent report has claimed that preoperative fistulography may be useful as 48 per cent of fistulograms (13 of 27) revealed either unexpected pathology or directly altered surgical technique, it may therefore be advantageous in patients with recurrent fistulae[103]. More recently, anal endosonography has been claimed to be accurate in the evaluation of anal fistulous abscess[104], but a prospective trial has shown that it is not yet useful clinically as it was technically unable to assess superficial, suprasphincteric, extrasphincteric, supralevator and infralevator tracks[85].

Secondary tracks are often diagnosed when induration or asymmetry between the right and left sides of the anorectum is palpated. Careful bidigital palpation will also define the relationship of the track to the anal sphincters and levators and help determine correct surgical technique. Sigmoidoscopy should be performed as part of the clinical routine to uncover associated underlying pathology[105] Barium enema or colonoscopy, however, need not be routinely carried out, as their diagnostic yield is low in relation to anal fistulae; they should be performed only when specifically indicated[105]. Very uncommonly, anal fistulae may mimic pelvic or intra-abdominal disease and other investigations may be necessary[106]. In selected cases (e.g. women with suspected previous obstetric trauma, patients with multiple previous laying open of anal fistulae, the very elderly, or patients with a high fistula) preoperative anal manometry may be useful in helping the surgeon to decide which surgical technique should be employed to prevent postoperative incontinence[25,74,107]. Indeed, a recent paper has advocated the routine use of manometry before operation to decide which surgical technique might improve function[86].

Management of the acute anorectal abscess

The term fistulous abscess was introduced in 1954 to stress that anal abscess and fistula are parts of a spectrum of the same disease process[108]. Traditionally, anorectal abscess has been treated by drainage either via a stab incision or saucerization. With the wide acceptance of the cryptoglandular aetiology of anal suppuration, primary or delayed fistulotomy with excision of the offending anal gland has been advocated[82,109–115]. Anorectal abscess is said to be cured permanently only when crypts and ducts are removed in addition to providing adequate drainage[81,82,115,116]. The high incidence (48–62 per cent) of recurrent abscesses or fistulae after simple incision and drainage is said to be reduced to 0–3 6 per cent following immediate fistulotomy[81,82,116–124] Proponents of the latter stress that the main reason for recurrence is an undiagnosed fistula present at the time of abscess drainage. The incidence of missed fistula during abscess drainage ranges from 18 to 95 per cent[29,99,116–125]. However, internal openings and fistula tracks may be difficult to demonstrate with safety during the acute phase of inflammation, and overzealous or inexperienced attempts at doing so may result in false passages or openings[112,126,127]. Indeed, complex supralevator and infralevator fistulous abscess has been said to be due to faulty surgery[81,82,109,128]. Furthermore, a prospective randomized trial has shown no statistically significant difference in recurrence rate between incision alone and incision followed by fistulotomy 3 days later[120]. The latter, however, is associated with a statistically significant higher incidence of flatus and incontinence, a longer hospital stay, and delayed healing. More than 50 per cent of patients with first-time anorectal abscess can be treated adequately by simple incision and drainage and so not all patients require division of a portion of sphincter muscle with the attendant risk of incontinence[115–117,126,129,130].

Fistulotomy in this situation may be followed by significant anal incontinence and should be used only if necessary[126,129,130]. Ischiorectal and intersphincteric abscesses have been reported to have a higher risk of recurrence than perianal abscesses[115–118]

It has also been shown that where a fistula is not found during the initial drainage, a subsequent search need be conducted only if culture of the pus obtained during the drainage procedure grows gut-specific organisms[100,131–133]. Anorectal abscesses which grow only skin-derived organisms are not associated with a fistula[100,131–133] and such abscesses need not be subjected to a second procedure. Drainage with primary suture under antimicrobial cover also has its advocates[134–138]. Shorter healing and hospital stay, and earlier return to work without any increase in recurrence rate, argue for its use[134–138]. A similar method using fistulectomy and primary closure under antibiotic cover has been used for chronic fistula, with good results[139], but until further trials are carried out drainage and suture will not be widely practised[140] Internal drainage of perianal abscess may be an useful alternative to percutaneous drainage, as the internal sphincter and glandular area may be removed without a skin wound[82,141,142]. Other workers suggest catheter drainage of the abscess cavity without immediate fistulotomy, claiming reliability, minimal morbidity, short hospitalization and early return to work as benefits[143,144]

Complicated forms of anorectal fistulous abscess

Three factors in complicated fistulae tend to perpetuate the disease process. First, the presence of a disease focus within the anal intramuscular gland or elsewhere within the anal canal; second, the constant contamination resulting from a high intrarectal pressure forcing intraluminal contents through the internal opening; and third, repeated surgery, which may create complicated tracks if not performed correctly. Complicated anorectal fistulous abscess includes supralevator abscess and infralevator horseshoe extensions.

The prevalence of supralevator fistulous abscess varies from 2 to 22 per cent[79,83,109,119,145–149]. Adequate drainage may be achieved endorectally or percutaneously. Endorectal drainage of supralevator extensions may require incision of the mucosa and submucosa, and both the circular internal muscle of the rectum and the circular internal sphincter along the whole length of the tract[142,150] (bearing in mind that total internal anal sphincter division may result in a degree of anal incontinence[151]). Supralevator abscesses or tracks found during percutaneous drainage of anorectal suppuration must be curetted and not laid open in order to prevent incontinence; free drainage should be maintained during healing using either setons or frequent digitation[147]. It is important to be certain of the origin of a supralevator fistulous abscess before drainage is attempted. A high intramuscular abscess or an intersphincteric abscess with supralevator extension may be drained endorectally, while a trans-sphincteric fistula with a translevator supralevator extension must be drained percutaneously[79]. If the former is drained percutaneously across the levator ani, or the latter drained endorectally, a suprasphincteric or an extrasphincteric fistula respectively will result, or if the puborectalis is carelessly divided, major incontinence will follow

Infralevator or ischiorectal horseshoe abscess is found in 9–38 per cent of cases of anorectal suppuration[91,93,152–156] In the posterior infralevator horseshoe abscess, the infection extends first through the posterior midline into the deep postanal space to spread laterally into the right or left ischiorectal fossa[157]. The deep postanal space is located between the tip of the coccyx posteriorly and the anal orifice anteriorly and lies between the superficial external anal sphincter muscle and the deeper levator ani Surgical access to this space is best achieved by a midline incision between the coccyx and the anus, spreading the superficial external anal sphincter to enter the space[153]. Preservation of the superficial external sphincter when the subcutaneous external sphincter has to be divided decreases anal deformity and incontinence[154]. Anterior infralevator horseshoe fistula erupts through the conjoint longitudinal muscle layer to enter the deep anterior anal space to spread laterally into the ischiorectal space[91,152,157]. In women, the deep anterior space extends superiorly into the rectovaginal septum and suppuration here may result in a rectovaginal fistula. Women are particularly prone to sphincter damage during surgery for anal fistula and extra care must be taken[158].

Although complicated fistulous abscesses are viewed with anxiety by many non-specialist surgeons, proper treatment should result in a low recurrence rate. Incision and drainage or primary fistulotomy may be used for the primary fistulous abscess. Setons can be used whenever laying open might interfere with anal continence. Secondary extensions may be drained by counter-incisions, complete laying open, insertion of various types of surgical drains, or by setons. Extensive laying open, however, is not necessary; it causes healing to be delayed, hospitalization to be prolonged, anal deformity and incontinence. Skin conservation should be practised as much as is possible; complete deroofing is not necessary to cure all complicated fistulae[159,160]. Multiple radial incisions may accomplish adequate drainage while preserving anal function and structure, even in complicated horseshoe fistula[161]. Defunctioning colostomy may be required occasionally, either because adequate fistulotomy will cause severe anal incontinence or because of severe anal sepsis. In the former case, a temporary defunctioning colostomy allows an adequate fistulotomy to heal the fistula as well as ensuring an easier subsequent sphincter repair[87] Sometimes patients with problematic fistulae after multiple operations may prefer a permanent colostomy. Indeed some patients may require proctectomy because of chronic disability if all else fails[87]. Very rarely sacrococcygectomy may be required to cure difficult presacral suppuration, especially in patients with established sacrococcygeal osteitis[162].

Massive anorectal suppuration

Anorectal abscess can precipitate extensive and severe infection which may lead to death, especially in the obese diabetic[149,163–168]. Surgeons must be specially careful when treating diabetics with anorectal suppuration. These patients may be septic or moribund on presentation or they may rapidly become so if not adequately treated. Spreading soft tissue infection of the perineum can be classified broadly into two groups[166]. The first group includes anorectal sepsis wherein the infection extends superficially around the perineum causing necrosis of skin, subcutaneous tissue, fascia or muscle. Affected patients may be recognized by perianal crepitation, erythematous indurated perianal skin, blistering or gangrene The second group includes sepsis wherein the preperitoneal or retroperitoneal spaces are also involved. Affected patients may have quite subtle signs, such as abdominal wall induration, tenderness or a vague mass Plain abdominal radiographs may show soft tissue gas in both groups and leucocytosis with a marked shift to the left may also be present in both. These two groups of patients require radical debridement of infected or necrotic tissue and the latter group may require exploratory laparotomy if intra-abdominal sepsis is suspected[166]. The use of a defunctioning colostomy alone is neither curative nor palliative; it is grossly inadequate[167,168] and may expose the already compromised patient to an unsurmountable bacterial load

Pus or necrotic material from the infected area must be cultured for anaerobes and aerobes. Clostridial and non-clostridial gas-forming organisms can be differentiated quickly by Gram staining the pus, with subsequent confirmation by culture[168]. Broad-spectrum antibiotics should always be used while awaiting sensitivity results. Mixed pathogens are usually grown, including Gram-negative aerobes such as *Escherichia coli* and Gram-negative anaerobes such as *Bacteroides fragilis*.

Common gas-forming organisms include clostridial species and anaerobic Gram-positive organisms such as *Peptococcus* and *Peptostreptococcus*[168].

Management of chronic anal fistula

Approximately 85–95 per cent of all anal fistulae are easy to treat[25,79,169]. Superficial, intersphincteric and low trans-sphincteric fistulae are readily managed by either classical laying open (fistulotomy) or by excision (fistulectomy) with a low recurrence rate and with minimal risk of postoperative incontinence[25,169–173]. The 5–15 per cent of anal fistulae that are difficult to manage must be dealt with differently and the remainder of this review is devoted to them.

Setons in the management of difficult fistula

The use of setons in the treatment of anal fistula is not new, having been described by Hippocrates and John of Ardene[1,3,4]. In 'modern' times, Allingham in 1875 was probably the first to write about the use of elastic ligatures to treat anal fistula[174]. Since then there have been numerous modifications of seton technique and material. Setons may be used in patients with complex fistula, high fistula, or difficult fistula where the landmarks have been so distorted that continence cannot be guaranteed if fistulotomy is performed (or if the surgeon opts to be cautious). They may be used in several ways. First, they may be applied loosely when used as drains, or as a stimulant to fibrosis around the track, or as markers to enable better postoperative assessment by outlining the track. Second, they may be applied tightly if the intention is to cut slowly through the track.

When used to promote fibrosis, setons act by holding the muscle ends together, thereby preventing separation of the anal sphincter muscle when fistulotomy is performed[175–178]. Kuypers managed ten patients with extrasphincteric fistula by a two-stage loose seton technique without any recurrence, although six patients had minor soiling and one suffered major incontinence[177]. In the first stage he placed a braided nylon seton around the puborectalis or the deep part of the external anal sphincter after laying open the more distal part of the track. Three months later, when the external wound had healed, the extrasphincteric part was laid open by dividing the seton-enclosed muscle. Ramanujam *et al.* treated 45 patients with suprasphincteric fistula by a two-stage fistulotomy technique based on the same principle[178]. In the first stage, the proximal (cephalad) half of the sphincter muscle was divided and a non-absorbable seton tied loosely around the intact distal half of the sphincter. Seven to 8 weeks later, when the external wound had healed or when adequate fibrosis was present, the distal sphincter was divided. There was only one recurrence (incidence 2 per cent) and although there was one instance of flatus incontinence, no faecal incontinence was seen.

Hanley used a rubber band seton for deep anterior and postanal fistulous abscess[176,179]. In acute cases, the seton initially was tied loosely around the subcutaneous external anal sphincter after the abscess had been drained. After about 3 weeks, when the wound had completely healed and inflammation had settled, the rubber band seton was tightened at 2-week intervals until the sphincter was severed. The seton initially acted as a drain, preventing premature closure of the deep anal space[159]. Hanley claimed that there was no discomfort and that anal canal deformity and incontinence was minimal[176,179].

Thomson and Ross, who view the seton mainly as a drain, have described a method of preserving the external anal sphincter completely in the treatment of high trans-sphincteric fistula[180]. During the initial operation an internal sphincterotomy is performed to lay open and drain the intersphincteric space. The primary fistula track may then be loosely encircled by monofilament 0 gauge nylon. About 6 weeks later, when adequate wound healing has occurred, the seton is removed. The external sphincter is laid open only if the fistula has not healed after removal of the seton. With this technique the fistula was cured while the external sphincter was preserved in 44 per cent of patients; only two of 12 patients in the series of Thomson and Ross were incontinent for liquid stool or flatus[180]. Kennedy and Zegarra, using a similar method, treated 32 patients with high trans-sphincteric or suprasphincteric fistula and achieved primary healing after seton removal in 78 per cent of 25 patients, with 33 per cent complaining of flatus incontinence and 25 per cent of mucus discharge; only one patient had occasional incontinence of liquid stool[181]. Seton material may be any type of foreign substance which can be inserted through the fistula track. Besides those already described, this includes Penrose drains[182], silk[80], adjustable non-absorbable sutures[183] and braided stainless steel wire[184].

Closure of the internal opening in the management of chronic high fistula

Elting in 1912 was probably the first to describe the treatment of high anal fistula using rectal mucosal advancement flaps[185]. Advantages of the mucosal advancement flap technique include a reduction in the duration of healing, no additional damage to the anal sphincter, no risk of deformity to the anal canal, and that it is a one-stage procedure if primary healing is achieved. The technique involves a total fistulectomy or coring out of the primary and secondary tracks, excision of the internal opening, and closure of the rectal defect with a mucosal advancement flap[186–194]. The mucosal suture line must be at a different level from the muscular suture line, as disruption of the latter is common[186]. Although called a 'mucosal' flap, the raised flap should include at least partial thickness of the rectal wall for added strength[186–188,193]. The width of the proximally placed flap base should be at least twice as long as the width of the apex to ensure an adequate blood supply[189,190,194]. A more cautious approach uses at least half the circumference of the rectal wall in forming the flap to reduce necrosis[193].

Aguilar *et al.* reported a series of 189 patients with anal fistula treated by the rectal mucosal advancement flap technique. There was a 1·5 per cent recurrence rate; 8 per cent had minor soiling, 7 per cent flatus incontinence, and 6 per cent incontinence of loose stool. None was incontinent of solid stool[187]. Some workers have used the technique on patients with acute abscess[187], while others stress that it should be reserved for chronic fistula without acute infection[189,194]. When an advancement flap is not technically feasible, direct suture or closure of the internal opening is said to give a satisfactory result[191]. Curettage of the external portion of the track as opposed to fistulectomy or excision is regarded by some as being technically easier, with similar functional results[193]. Defunctioning colostomy or ileostomy is not a necessary prerequisite in the mucosal advancement flap technique[186–194].

Other techniques for difficult anal fistula

Polymethylmethacrylate copolymer beads have been used to prevent postoperative infection and enhance rapid wound healing after high fistulectomy and primary wound closure[195]. The effect may be due to long-term drainage provided by the presence of the string of beads left in the surgical cavity[196]. Ayurvedic treatment of fistula *in ano* using the insertion of a thread impregnated with a caustic solution to destroy the fistula track and therefore perform chemical fistulectomy appears promising, although it is practised in only a few third world countries[197,198]. The carbon dioxide laser can also be used to vaporize the granulation tissue or track wall in high anal fistulae and may allow fistulectomy without destroying excessive sphincter muscle[199,200]. Rerouting of the high anorectal fistula by transposing the extrasphincteric portion of the track into the intersphincteric position, with primary sphincter repair and subsequent fistulotomy of the transposed track, has largely been given up as the technique is difficult and the long-term results poor[201].

Malignant transformation in chronic anal fistula

Rosser in the first report of a series of cases of chronic anal fistula with malignant transformation established three criteria to help decide whether the carcinoma originated from the fistula or not[202]. First, the fistula should antedate the cancer significantly. Second, there should be no synchronous tumour in the anorectum or colon unless secondary to direct invasion from the cancer in the fistula. Third, the internal opening of the fistula should be into the anal canal and not into the tumour itself[202]. Since that time, about 150 cases of carcinoma in anal fistulae have been described[202–217], and although most represent fistulous degeneration of malignancy within the anorectum, some fulfil Rosser's criteria and probably arose by malignant change within a chronic fistula track. There is evidence that some of these lesions arise within a congenital malformation or duplication of the hindgut[205]. Granulation tissue or multiple biopsies of the fistula track or the fistulectomy specimen must be examined histologically in long-standing fistulae, especially if mucinous discharge or mucin globules are seen during surgery. These tumours are slow growing, locally invasive and usually are of low-grade differentiation. Metastases occur most frequently to the inguinal region[212]. Radical resection of the anorectum offers the only hope of cure, as local excision results in a high rate of recurrence[212].

Anal fistula in infants

Anal fistula in early infancy is due to congenital abnormality of the anal glands[218]. Theories advanced to explain this include excessive intrauterine androgens causing abnormal anal glands[219], ectopic epithelial cells[220], failure of fusion of genital folds[221], irregularly thickened dentate line with deep anal crypts capable of trapping bacteria[222], and congenital sinus due to anorectal malformation[223]. The vast majority of patients are boys less than 12 months old[218–223]. Management is along adult lines. The majority are intersphincteric fistulae and are therefore easily treated[218–223]. Shafer *et al.* advise cryptotomies in addition to the usual fistulotomy in accord with their theory regarding infantile anal fistula[222].

Conclusion

Anal fistula is a common cause of chronic irritation. Treatment failure rates may be decreased by a good appreciation of normal anorectal anatomy and fistula pathoanatomy as well as a wide and practical knowledge of the possible treatment regimens. Identification of the patient at risk of postoperative anal incontinence, or of the difficult or high fistula, should allow treatment in a specialist proctology unit. The paucity of well controlled trials on the management of anal fistula is unfortunate; such trials need to be carried out so that the various modalities of treatment may be more accurately assessed and understood.

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Management variability in surgery for colorectal emergencies

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A prospective study was made of 92 patients who underwent emergency colorectal surgery during a 1-year period. A dedicated emergency theatre allowed half of the patients to be operated on between 09.00 and 17.00 hours with greater seniority of operating surgeons. The overall mortality rate was 14 per cent and the primary resection rate was 79 per cent. The mortality rate was 12 per cent for right-sided resection with anastomosis and 24 per cent for left-sided resection without anastomosis, including those undergoing Hartmann's procedure which had a 35 per cent mortality rate. Immediate left-sided anastomosis was performed safely in all 14 patients in whom it was attempted. Firms headed by consultants with and without a special interest in colorectal disease made differing use of primary resection and immediate anastomosis (67 versus *41 per cent,* $\mathrm{P} < 0{\cdot}05$*) and Hartmann's (7* versus *25 per cent,* $\mathrm{P} < 0{\cdot}05$*) and non-resectional (15* versus *29 per cent,* P *not significant) procedures. Retrospective surveys of perioperative deaths examine inadequate management and subsequent mortality rates, but do not reveal the significant morbidity rate that occurs in survivors. This audit revealed significant differences in the management of patients with colorectal emergencies between firms headed by specialist and non-specialist consultants. In order to minimize these differences we believe that recent advances in colorectal practice should be included in the training of all surgeons.*

In 1985 Koruth *et al.*[1] presented a large series of patients admitted with colorectal emergencies under a single consultant with a particular interest in colorectal disease. They suggested that when emergency surgery was required it was advantageous to perform primary resection and in selected cases immediate anastomosis. In 1988 Mealy *et al.*[2] advocated a similar policy.

In 1987 the report was published of the Confidential Enquiry into Perioperative Deaths (CEPOD)[3], highlighting common areas of inadequate management in the perioperative period of elective and emergency surgery. Areas of criticism were lack of supervision of junior staff, the failure of juniors to seek advice, deficiencies in preoperative assessment and resuscitation, and the performance of operations on already moribund patients.

In this hospital colorectal surgical emergencies are managed by all of the 'on-take' firms. It was of particular interest to see whether there was any difference in management of patients between those admitted under consultants who had or did not have a special interest in colorectal disease.

A prospective study of all patients undergoing emergency colorectal surgery over a 1-year period was made.

Patients and methods

For a period of 1 year all patients who underwent urgent or emergency colorectal surgery in the John Radcliffe Hospital, Oxford were studied prospectively.

Patients were included who satisfied any one of the following criteria. First, the patient was admitted as an emergency and underwent early surgery for colorectal pathology after a period of resuscitation. Second, the patient was admitted as an emergency and underwent colorectal surgery after a period of failed conservative management Third, the patient was admitted electively and during this admission developed an acute colorectal condition requiring urgent surgery.

A standard pro forma was available in the operating theatre. This covered the preoperative assessment, vital signs, basic laboratory results, indications for surgery, operator seniority, start time and duration of procedure, operative findings and the procedure performed. The surgeon defined the degree of peritoneal sepsis in a standardized way to enable comparison with other series[4]. A distinction between diffuse serous and diffuse purulent peritonitis was not made. The theatre register was checked daily to see whether any operations had been performed that might be suitable for inclusion. The ward was then visited to ensure that, if appropriate, the data collection had been started and to allow a continuing review of management and complications

After the operation, details were recorded of morbidity, death in hospital and up to 30 days after operation, specimen histology and the length of hospital stay before discharge to home or convalescence

Statistical analysis was by the Mann–Whitney *U* test and Fisher's exact test as appropriate.

Results

Clinical presentation

A total of 92 patients satisfying the criteria for inclusion were admitted during the study period (*Figure 1*). Forty-one patients were admitted under the care of consultants with a special

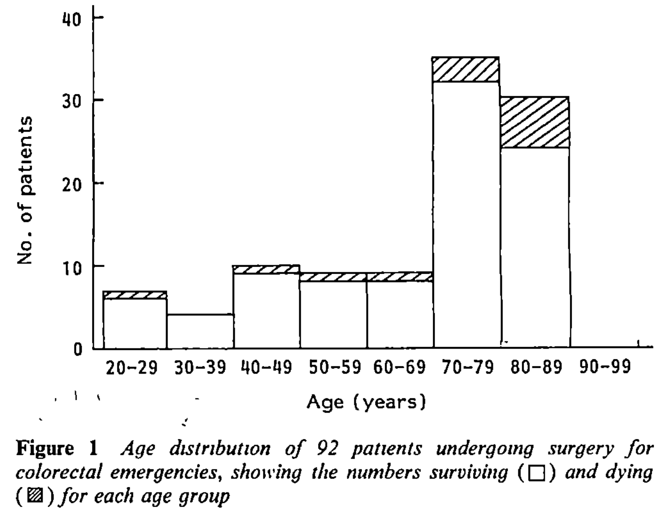

Figure 1 *Age distribution of 92 patients undergoing surgery for colorectal emergencies, showing the numbers surviving* (□) *and dying* (▨) *for each age group*

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Table 1 *Final diagnosis, age and incidence of peritoneal sepsis and obstruction in 92 patients undergoing emergency colorectal surgery*

	No. of patients	Mean (range) age (years)	Peritoneal sepsis*	Obstruction*
Diverticular disease	27	74 (36–85)	24 (89)	3 (11)
Colonic carcinoma	27	70 (35–89)	9 (33)	23 (85)
Inflammatory bowel disease	14	47 (24–82)	1	2
Colonic bleeding	8	63 (43–82)	0	1
Colonic volvulus	6	60 (26–79)	1	6
Pseudo-obstruction	3	74 (68–84)	0	3
Iatrogenic perforation	3	64 (31–82)	2	0
Other	4	80 (72–85)	2	2
Total	92	66 (24–89)	39 (42)	40 (43)

*Values in parentheses are percentages

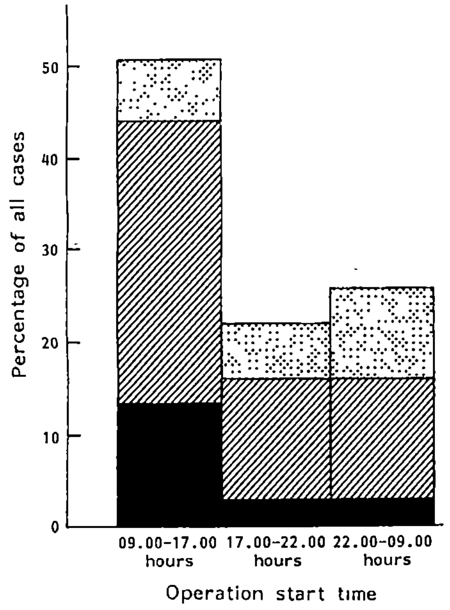

Figure 2 *The percentage of cases undergoing surgery, divided according to operation start time. Within each time period the grade of the most senior surgeon recorded as present is shown: consultant (■), senior registrar (▨); registrar (□)*

interest in colorectal disease and the remainder were under general surgeons with other principal interests. The final diagnosis of the 92 patients based on clinical findings and histology is shown in *Table 1*.

The 14 patients with inflammatory bowel disease admitted as emergencies were all subsequently managed on special interest firms, but the other patients were managed by the admitting team. Eight patients underwent surgery for severe colonic haemorrhage. The policy for patients with life-threatening colonic bleeding was to proceed directly to on-table colonoscopy[5]; this was performed in six of the eight patients The source of bleeding was right-sided angiodysplasia in four patients, a solitary caecal ulcer in one and was not identified in one patient with widespread diverticular disease. The source of bleeding was known in two patients and they proceeded directly to surgery. Of the six patients with colonic volvulus, this was caecal in three and sigmoid in three. The four miscellaneous cases were a perforated solitary caecal ulcer, a caecal resection for appendicitis and two cases of gynaecological malignancies causing colonic obstruction.

Peritoneal sepsis was present at laparotomy in 39 cases (42 per cent). This was localized with minimal contamination in two cases after iatrogenic perforation, there was a phlegmon in four, a localized abscess in 14, localized free faeces in one, generalized serous or purulent peritonitis in 12, and generalized faecal peritonitis in six. Twenty-four of the 27 patients with diverticular disease had sepsis in contrast with nine of the 27 patients with colonic carcinoma ($P < 0.001$).

Resuscitation, operative timing and seniority

The majority of patients (84 of 92; 91 per cent) were resuscitated as shown by the criterion of systolic blood pressure greater than 100 mmHg at the time of induction of anaesthesia. Four of the eight patients with colonic haemorrhage were significantly hypotensive All the other hypotensive patients were showing signs of systemic sepsis.

Forty-seven (52 per cent) of the operations were started between 09.00 and 17.00 hours, 20 operations (22 per cent) between 17.00 and 22.00 hours, and 24 operations (26 per cent) between 22.00 and 09.00 hours. The operator grade varied with the different operation start times. The best chance of a consultant being present for the operation (12 of 47 cases) was between 09.00 and 17.00 hours. Conversely if the operation was performed between 22.00 and 09.00 hours the registrar (nine of 24 cases) was more likely to be operating alone (*Figure 2*). However, of the 13 patients who died, none had their operation performed between midnight and 09.00 hours (*Table 2*).

The most senior surgeon recorded as present in theatre was a consultant in 20 cases (22 per cent), senior registrar in 51 (57 per cent) and registrar in 19 (21 per cent). The corresponding figures for the anaesthetist were 14 (16 per cent), 31 (35 per cent) and 43 (49 per cent). Parts or all of some operations were performed by a more junior assistant.

Mortality

There were 13 deaths (14 per cent; *Table 2*). Twelve of these patients were operated on by a consultant surgeon or senior registrar. *Figure 1* shows the age distribution of survivors and of those who died. There was a significant correlation between increased age and death in patients with diverticular disease and colonic carcinoma. Continuing abdominal sepsis and its systemic manifestations was the major cause of death in ten patients. Two patients with formal caecostomies for pseudo-obstruction were not adequately decompressed by this procedure. The single clinically detected anastomotic leak (one of 39) after ileorectal anastomosis led to the death of the patient.

Complications in survivors

Eighteen patients (23 per cent) suffered major non-fatal complications and 20 (25 per cent) suffered minor complications. Complications occurred in 18 of 25 patients with diverticular disease in contrast to nine of 24 patients with cancer of the colon ($P = 0.032$). Major complications in survivors included chest infection (four cases), deep vein

Table 2 *Details of 13 patients who died after surgery*

Age (years)	Diagnosis	Procedure	Surgeon	Anaesthetist	Cause of death	Start time	Time to death (days)
54	Bleeding	Right hemicolectomy	SR	C	Pulmonary embolus present before operation	17.00	5
89	Cancer	Hartmann's operation	SR	R	Septicaemia	15.00	2
83	Diverticular disease	Hartmann's operation	C	C	Septicaemia	16.30	<1
79	Diverticular disease	Hartmann's operation	SR	SR	Septicaemia	22 30	<1
73	Crohn's disease	Hartmann's operation	SR	SR	Septicaemia	13.25	4
82	Crohn's disease	Hartmann's operation	SR	C	Septicaemia	12.30	7
86	Cancer	Right hemicolectomy	R	R	Pneumonia	19 00	21
47	Bleeding	Subtotal colectomy	SR	R	Septicaemia	11 00	14
81	Cancer	Hartmann's operation	SR	SR	Abdominal sepsis	12.15	35
84	Pseudo-obstruction	Caecostomy	C	SR	Pneumonia	22.00	21
26	Volvulus	Ends exteriorized	SR	SR	Septicaemia	16 45	5
68	Pseudo-obstruction	Caecostomy	SR	C	Abdominal sepsis	11.15	31
78	Bleeding	Subtotal colectomy	SR	R	Sepsis, anastomotic leak	11.45	16

C, consultant; SR, senior registrar, R, registrar

Table 3 *Details of procedure performed and incidence of sepsis and obstruction, complications in survivors and number of deaths*

Procedure		No. of patients	Sepsis	Obstructed, no sepsis	Complications		Deaths
					Minor only	Major	
Primary resection (73 of 92; 79 per cent)							
With anastomosis (39 of 73)	Right and extended right hemicolectomy	23	4	13	7	3	2
	Ileorectal	2	1	0	0	0	1
	Sigmoid colectomy	14 (st 5)*	8	6	4	3	0
No anastomosis (34 of 73)	Right hemicolectomy	1	–	1	0	0	0
	Subtotal colectomy	11	1	0	1	2	1
	Sigmoid colectomy	3	3	0	1	1	1
	Hartmann's operation	17	16	1	4	6	6
	Proctocolectomy	2	0	0	0	0	0
No primary resection (19 of 92)	Colostomy	12	4	8	2	4	0
	Caecostomy	2	0	2	–	–	2
	Lavage and drain	4	4	0	2	0	0
	Internal bypass	1	–	1	0	0	0

*st, Patients with covering stoma. One patient had two minor complications and one had two major complications

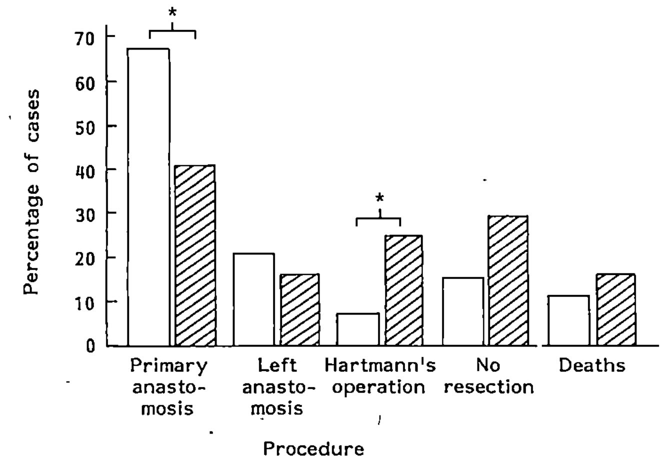

Figure 3 *The percentage of patients operated on under consultants with* (☐) *and without* (▨) *a special interest in colorectal disease who underwent primary resection with immediate anastomosis* (*primary anastomosis*), *left-sided resection and immediate anastomosis* (*left anastomosis*), *Hartmann's operation or non-resectional procedure* (*no resection*), *and the percentage of patients on each type of firm who subsequently died. The 14 patients with inflammatory bowel disease were excluded because they were all admitted under or were transferred to special interest firms.* *$P < 0.05$ (*Fisher's exact test*)

thrombosis (three), myocardial infarction (two), stoma problems (three), superficial wound dehiscence (two), early adhesive obstruction (one), stroke (one), subphrenic abscess (one) and axillary vein thrombosis (one). The most common minor complications were chest infection (nine), wound infection (seven) and urinary tract infection (five) Overall, chest infection occurred in 16 per cent of cases and wound infection in hospital in 11 per cent.

Operative details

In the operating theatre all patients received cefuroxime and metronidazole and seven patients also received gentamicin. The details of the procedures performed and the incidence of peritoneal sepsis and obstruction are summarized in *Table 3*. The majority of resectable obstructing lesions in the right and transverse colon were treated by right or extended right hemicolectomy. Primary resection was performed in 73 cases (79 per cent) with an overall mortality rate of 12 per cent. Resection and immediate anastomosis were performed in 39 cases, with a mortality rate of 8 per cent. The anastomosis was ileocolic in 25 cases with a mortality rate of 12 per cent and colorectal in 14 with no mortality. For those undergoing primary resection but without anastomosis (34 of 73) there was a 24 per cent mortality rate. Nineteen patients underwent non-resectional operations on the colon with no deaths.

Operative differences between firms

All 14 patients with inflammatory bowel disease underwent primary resection without anastomosis after referral to consultants with a special interest in colorectal disease, and therefore these patients are not considered further In comparable operative groups 18 of 27 patients admitted under special interest firms underwent primary resection with immediate anastomosis in contrast to 21 of 51 patients ($P < 0.05$) admitted under consultants without this interest. On special interest firms a lower proportion of patients underwent Hartmann's procedure than on firms with no special interest (two of 27 *versus* 13 of 51, $P < 0.05$), as was the case for non-resectional procedures (four of 27 *versus* 15 of 51, no significant difference) (*Figure 3*). A greater percentage of the operations were performed by registrars on firms with no special interest (32 *versus* 14 per cent). The senior registrar on special interest firms performed a primary resection and anastomosis in 70 per cent of cases and a non-resectional procedure in 5 per cent, compared with 48 and 28 per cent respectively on firms with no special interest.

Discussion

This study reviews the management and outcome of colorectal emergencies during a 12-month period in a district which serves a population of 546 000.

Twenty-seven patients underwent surgery for diverticular disease. This confirms the increase in emergency surgery for this condition seen in our hospital over the period 1982–1985[6] and is probably related to the ageing population[7]. The incidence (89 per cent) and severity of peritoneal contamination was higher than in other reported series[4]. This may be explained by the increasing use of conservative management for this condition, such as aggressive antibiotic therapy with computed tomographically guided drainage of residual abscess cavities. Such changes select only those with more severe pathology for surgery, but our study was not designed to include cases not operated on. Despite the severity of peritoneal sepsis found there were only two deaths (7 per cent) in this group.

Twenty-seven patients underwent surgery for colonic carcinoma. As expected 85 per cent were obstructed but an unexpectedly high proportion (33 per cent) also had peritoneal sepsis compared with 11 per cent in the large bowel cancer project[8]. Peritonitis was present on admission to hospital. Because elective surgery carries a greatly reduced mortality rate and is more likely to allow a restorative procedure, these patients clearly need to reach hospital earlier.

Eight patients underwent surgery for severe life-threatening colonic haemorrhage. It has been management policy to treat these patients after resuscitation by on-table colonoscopy and surgery[5]. Patients with moderate bleeding were managed conventionally by angiographic localization, colonoscopic injection and angiographic obliteration as appropriate. The delay caused by, and inadequate resuscitation during, angiographic localization before surgery in shocked patients may be associated with an increased mortality rate[9]. Three of the eight patients operated on died; death was due to the severity of the presenting pathology in two and to anastomotic failure in one patient who underwent a subtotal colectomy and ileorectal anastomosis after failure to localize the source of bleeding.

All the patients with pseudo-obstruction treated by surgery were under non-special interest firms. The management of these patients was unsatisfactory and indicates a lack of a defined protocol for management of this condition. These patients should have undergone more rigorous preoperative investigation to make the diagnosis by either colonoscopy[10,11] or contrast enema.

The majority of patients in this series were well resuscitated as judged by the systolic blood pressure at induction of anaesthesia. A considerable number of cases were delayed overnight and more than half of the procedures were started between 09.00 and 17.00 hours, and 74 per cent between 09.00 and 22.00 hours. In the CEPOD report[12] there was little evidence that delay contributed to a fatal outcome. Indeed, undue haste to operate was more likely to be detrimental, because if any salt and water deficit is not replaced before operation the additional stress of anaesthesia and surgery may lead to cardiac and renal dysfunction. The availability of a staffed emergency theatre throughout the day encouraged surgeons to delay cases until resuscitation was complete, and we believe this was beneficial.

Some non-essential cases were started at night despite the availability of an emergency theatre the next day. Several possible explanations exist for this. First, it is still perceived by some that delay will always be associated with a worsened outcome. Second, even if an operating list is made available the next day, the surgical firm is often not available owing to commitments to routine outpatients or operating lists. Additionally, the trainee may feel that he or she will lose the opportunity to operate if the case is delayed. This is particularly so with colorectal cases which are often time-consuming and may be taken over by a more senior colleague.

The CEPOD report criticized the lack of seniority of some of the surgeons operating on patients who subsequently died Seniority decreased with the later start times. However, in patients in this series who died, 12 of 13 were operated on by a consultant or senior registrar.

The 14 per cent mortality rate observed is similar to that found in other large series of similar patients, 19·2 per cent[1] and 14·3 per cent[2]. The cause of death in most patients was disease progression, peritoneal sepsis and multiorgan failure. In several of these cases the patient could have been identified as being fatally compromised before operation and unnecessary surgery might have been avoided. Significant morbidity occurred in survivors, but postoperative abdominal sepsis was rare, with a single patient developing a liver abscess and subphrenic collection (1 per cent). This would suggest that failure to control the intra-abdominal sepsis at the time of surgery is usually fatal.

It is now well established that primary resection of the diseased segment of bowel can be performed in most cases[1] and this was done in 79 per cent of the patients with a 12 per cent mortality rate. Right-sided resection and anastomosis can be safe even in the presence of sepsis, but the risk of complications and death is often underestimated in these patients[13,14]. In our series 25 patients underwent an ileocolic anastomosis with a 12 per cent mortality rate. Left-sided resection with immediate anastomosis in the presence of peritoneal sepsis is controversial. However, in selected cases this can be performed safely[2,4], particularly after the use of intraoperative antegrade colonic irrigation[15,16]. The absence of anastomotic complications and no deaths in 14 patients undergoing primary anastomosis, including eight with peritoneal sepsis, lends support to this policy. However, this type of procedure should still be used with caution and is not suitable for all patients[17].

The mortality rate for all patients who underwent a primary resection without anastomosis was 24 per cent. Hartmann's operation is recommended for patients with a perforated sigmoid colon[18,19] but this often failed to eradicate sepsis with a consequent high mortality rate (35 per cent) and a very high complication rate in survivors (ten of 11). The potential problems with this procedure have been reported previously[6].

Sixty-seven per cent of patients admitted to special interest firms underwent primary resection and anastomosis compared with 41 per cent on firms without a special interest On special interest firms a much lower percentage of patients underwent Hartmann's procedure. There were no obvious differences between the two groups in the age, diagnosis or severity of pathology to explain these figures.

The differences between firms are clinically significant only if the outcome is changed in similar patients, and this is most likely to be evident in patients with left-sided colonic pathology. In this series, some patients underwent Hartmann's procedure on a non-specialist firm when a similar patient on a special interest firm would have undergone immediate anastomosis. Six of the 17 patients who underwent Hartmann's procedure died, in contrast to none of the 14 patients in whom immediate anastomosis was performed. This difference in mortality rate could not be explained entirely by case selection. Furthermore, many patients are left with a permanent stoma after Hartmann's procedure, which is a considerable morbidity in its own right, and those who undergo a reversal of this procedure are exposed to a considerable extra risk of morbidity and mortality and an extended period of hospitalization.

In most district hospitals it is not practical to arrange for all patients with colorectal emergencies to be operated on under a special interest firm. If surgeons without a special interest in colorectal problems are to continue managing these patients, there is a continuing need to disseminate the more recent advances to surgeons in training. However, this is becoming increasingly difficult with the trend towards specialization at senior registrar level. In major centres a case can be made for specialist colorectal emergency rotas such as exist for vascular surgery[20].

To address some of the deficiencies within the existing framework, the provision of a dedicated emergency theatre encourages a larger proportion of cases to be operated on during normal working hours, and with this come improvements in patient management. Operating time can then be used to teach and to allow the optimal procedure to be performed. With the commitment towards a larger proportion of the workload being transferred to an expanded consultant grade, this may bring further improvements along the lines recommended in the CEPOD as well as the opportunity to provide a proper training for future surgeons who will deal with these difficult patients.

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Laparoscopic approach to Meckel's diverticulectomy

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The arrival of videoendoscopy has facilitated a wide range of endoscopic operative procedures across a variety of surgical disciplines, including gynaecology, otorhinolaryngology, orthopaedics and most recently general surgery. Laparoscopic cholecystectomy is currently the most common major abdominal operation performed endoscopically[1]. Increasing familiarity with this new technique has resulted in a growing list of operations that can be performed with the aid of the laparoscope. The first laparoscopic approach to performing Meckel's diverticulectomy for acute inflammation is described.

Technique

A 28-year-old man with a previous appendicectomy presented with acute abdominal pain A diagnostic laparoscopy was performed using a 10-mm trocar inserted below the umbilicus and a 5-mm trocar in the right iliac fossa. This revealed a swollen and inflamed Meckel's diverticulum The diverticulum and its attached loop of small intestine were brought onto the surface of the abdominal wall (*Figure 1*) by pulling the diverticulum into the 10-mm trocar at the umbilicus and then removing the trocar from the abdominal cavity A 3-mm extension to the incision was required to allow the loop of small intestine to come onto the surface With the loop so exteriorized (*Figure 2*), the Meckel's diverticulum was then simply removed using a TA55 stapler (Auto Suture, Dublin, Ireland) and the small bowel was replaced into the peritoneum The two wounds were closed with subcuticular absorbable sutures The patient recovered full mobility the following day and was discharged home on a normal diet on the third day after operation Histology confirmed the presence of an acutely inflamed Meckel's diverticulum, containing gastric-type epithelium.

Discussion

The advantages of laparoscopy over laparotomy include rapid recovery of full muscle function and the lack of postoperative pain In this patient, the laparoscope was used to make a diagnosis and to facilitate a standard operation by exteriorizing the relevant segment of small intestine. With the introduction of laparoscopic stapling devices, Meckel's diverticulectomy could be performed entirely within the peritoneal cavity under laparoscopic control, but this would probably not confer any great advantage over the procedure adopted in this case. The use of diagnostic laparoscopy is recommended in all patients with atypical abdominal pain for the purposes of establishing an accurate diagnosis and to perform definitive surgery where feasible.

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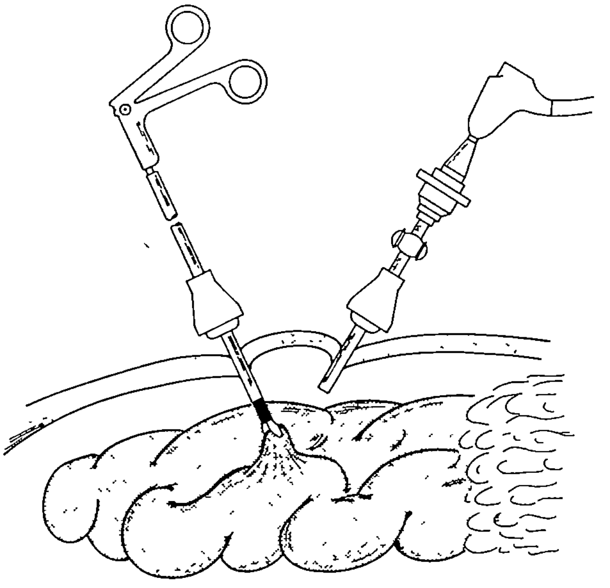

Figure 1 *At laparoscopy, a grasping forceps was placed onto a Meckel's diverticulum to pull it into a 10-mm laparoscopic trocar and allow exteriorization of the diverticulum and its attached loop of small intestine*

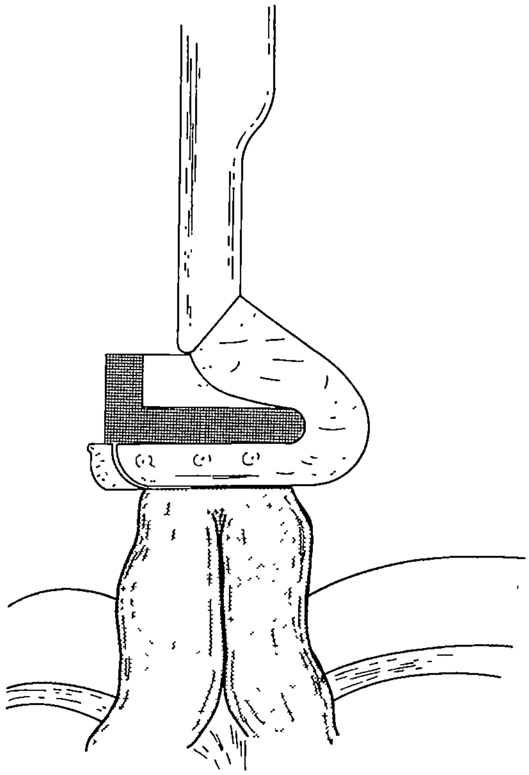

Figure 2 *A stapling instrument was placed across the base of the exteriorized Meckel's diverticulum, allowing simple transection and closure*

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Long-term changes in muscle free amino acid levels after elective abdominal surgery

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Characteristic changes in the pattern of muscle free amino acids are seen on the third day after elective surgery. The time course of the restoration to normal levels in uncomplicated cases has not been established before. Seven metabolically healthy patients undergoing cholecystectomy were studied. Muscle biopsy specimens and plasma samples were taken before operation and on days 3, 10, 20 and 30 after surgery. The level of total free amino acids in skeletal muscle decreased and the concentrations of branched chain and aromatic amino acids increased on day 3. The original levels were found to be restored on day 10 after surgery. A decrease in glutamine of 38 per cent ($P < 0.001$) *was seen on day 3, of 20 per cent* ($P < 0.05$) *on day 10 and of 22 per cent* ($P < 0.05$) *on day 30, compared with preoperative values. These results constitute a baseline for future studies in which the impact of nutritional and pharmacological therapies is to be evaluated beyond the immediate postoperative period.*

Protein metabolism after trauma is characterized by catabolism in muscle tissue and a negative whole body nitrogen balance. There is an export of amino acids from peripheral tissues to the splanchnic area for use as energy substrates, for gluconeogenesis, ureagenesis, and for the synthesis of priority proteins. Hence, free amino acids are the currency of protein metabolism.

Trauma, including elective surgery, leads to characteristic changes in muscle amino acid concentrations, although changes in plasma amino acid levels are less consistent[1,2]. Decreases in muscle glutamine and the basic amino acids, together with an increase in levels of the branched chained amino acids (BCAAs; isoleucine, leucine, valine) as well as phenylalanine, are seen. These changes have been reported on the third to fifth day after a variety of surgical procedures. Plasma free amino acids are often normal at this time. Obviously, the pattern of muscle free amino acids reflects changes in protein and energy metabolism in muscle as well as altered amino acid metabolism. The non-uniform temporal development of the altered muscle amino acid pattern has recently been established[3]. However, the time course for recovery of these changes has not been elucidated.

Following elective surgery, protein synthesis as estimated by analysis of ribosomes is still not restored to normal 30 days after operation[4]. Postoperative fatigue syndrome persists for a similar period of time. In order to establish a baseline for future studies in which efforts will be made to improve postoperative performance by nutritional or pharmacological means, the natural course of muscle free amino acid recovery was recorded on five occasions during 30 days after operation in seven patients who had undergone elective abdominal surgery.

Patients and methods

Seven metabolically healthy patients admitted for elective cholecystectomy participated in the study. Characteristics of the patients and of the surgical procedure are summarized in *Table 1*.

Patients were examined in the morning after overnight fasting before the operation and on the third, tenth, 20th and 30th day after surgery. Blood samples and muscle biopsy specimens were taken before surgery immediately after the induction of general anaesthesia and on days 3, 10, 20 and 30 after the operation after injection of local anaesthetic into the skin (Citanest (prilocaine) 10 mg ml^{-1}, Astra, Södertälje, Sweden). The operation took place on the day after admission after overnight fasting. All patients were given general anaesthesia with sodium thiopental, fentanyl, suxamethonium, droperidol, pancuronium, and oxygen–nitrous oxide. On the day of the operation patients were given intravenously a total of 3000 ml of an electrolyte solution (Na^+, 70 mmol l^{-1}; Cl^-, 45 mmol l^{-1}; acetate, 25 mmol l^{-1}) containing 2·5 per cent glucose (Rehydrex, Pharmacia Infusion, Uppsala, Sweden). Oral intake started on the first day after operation and gradually increased at will. The normal intake of the subjects was reached within 1 week after the operation. Details of the nutritional regimen are given elsewhere[4]. Patients were mobilized on the first day after surgery and no prophylactic pharmacological antithrombotic treatment was given.

Table 1 *Characteristics of the patients and surgical procedure*

Sex ratio (M:F)	2:5
Age (years)	51(5)
Weight (kg)	63(5)
Height (cm)	167(4)
Operating time (min)	90(3)
Intraoperative blood loss (ml)	143(36)

Values for continuous variables are mean(s.e.m.)

The nature and purpose of the experimental procedure and the risks involved in it were explained to the patients before obtaining their consent. The research protocol was approved by the ethical committee of the Karolinska Institute.

Percutaneous muscle biopsy specimens were taken from the lateral portion of the quadriceps femoris muscle using a Bergstrom biopsy needle[5]. Approximately 20 mg muscle tissue was dissected carefully to remove visible fat and connective tissue and then weighed three times in 24 s on an automatic electrobalance (Cahn 29; Cahn Instruments, Cenato, California, USA). Within 5 min of sampling the muscle specimens were frozen in liquid nitrogen and stored at −80°C for later analysis. The muscle specimens were homogenized and precipitated in sulphosalicylic acid and the concentration of amino acids in plasma and in skeletal muscle tissue determined by ion exchange chromatography[6] using an automated amino acid analyser (Alpha Plus; LKB, Bromma, Sweden) employing DC-6 ion exchange resin (Durham, California, USA) and lithium citrate buffers. The concentration of the muscle free amino acids was determined per kilogram wet weight of muscle.

Values are given as mean(s.e.m.) except where otherwise indicated. Student's paired *t* test was used to compare the different observations[7].

Results

Muscle biopsies were performed before operation and on days 3, 10, 20 and 30 afterwards in seven patients undergoing elective cholecystectomy. The concentration of total free amino acids

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Table 2 *Concentration of free amino acids in skeletal muscle before elective abdominal surgery and on days 3, 10, 20 and 30 after operation* (n = 7)

		After operation			
Amino acid	Before operation	Day 3	Day 10	Day 20	Day 30
Taurine	14·14(0·83)	12·96(1·10)	14·49(1·37)	15·1(1·87)	14·81(1·01)
Aspartate	0·81(0·06)	0·76(0·06)	0·87(0·04)	0·82(0·09)	0·74(0·11)
Threonine	0·64(0·05)	0·69(0·02)	0·60(0·05)	0·59(0·04)	0·67(0·04)
Serine	0·76(0·09)	0·80(0·06)	0·78(0·10)	0·74(0·05)	0·76(0·07)
Asparagine	0·36(0·06)	0·50(0·05)†	0·36(0·05)	0·25(0·03)	0·30(0·03)
Glutamate	2·30(0·16)	1·45(0·11)†	2·61(0·17)	2·75(0·27)	2·72(0·19)
Glutamine	14·41(0·75)	8·96(0·61)§	11·44(0·86)†	12·48(1·04)	10·78(0·70)†
Glycine	1·36(0·10)	1·34(0·08)	1·44(0·06)	1·46(0·13)	1·54(0·13)
Alanine	3·23(0·23)	2·95(0·13)	2·92(0·27)	2·64(0·34)	3·08(0·21)
Valine	0·35(0·02)	0·42(0·03)	0·36(0·05)	0·29(0·01)†	0·32(0·02)
Methionine	0·04(0·01)	0·05(0·01)	0·07(0·03)	0·04(0·01)	0·04(0·01)
Isoleucine	0·08(0·03)	0·14(0·02)‡	0·07(0·01)	0·08(0·02)	0·08(0·02)
Leucine	0·24(0·02)	0·31(0·02)	0·23(0·02)	0·21(0·01)	0·24(0·02)
Tyrosine	0·11(0·02)	0·17(0·02)	0·14(0·02)	0·12(0·02)	0·14(0·02)
Phenylalanine	0·09(0·01)	0·14(0·01)†	0·12(0·02)	0·09(0·01)	0·12(0·01)
Ornithine	0·39(0·05)	0·35(0·03)	0·42(0·05)	0·39(0·03)	0·38(0·02)
Lysine	1·27(0·07)	1·23(0·13)	1·13(0·09)	1·11(0·09)	0·97(0·09)
Histidine	0·59(0·05)	0·48(0·03)	0·44(0·06)	0·47(0·05)	0·45(0·05)
Carnosine	5·82(0·97)	5·23(0·98)	4·46(1·01)	4·62(0·74)	3·84(0·83)†
Arginine	0·59(0·07)	0·51(0·08)	0·44(0·06)	0·51(0·07)	0·42(0·07)
Sum of					
Aromatic amino acids	0·21(0·02)	0·31(0·03)†	0·26(0·03)	0·20(0·02)	0·25(0·03)
Branched chain amino acids	0·67(0·06)	0·86(0·05)†	0·66(0·07)	0·56(0·03)	0·64(0·05)
Basic amino acids	2·44(0·18)	2·22(0·21)	2·02(0·16)	2·09(0·16)	1·84(0·19)
Essential amino acids	2·71(0·15)	2·98(0·15)	2·58(0·20)	2·37(0·13)	2·44(0·11)
Total amino acids*	27·61(1·34)	21·26(0·82)‡	24·44(1·18)	24·44(1·63)	23·74(0·91)

Values are mean(s.e.m.) expressed in mmol kg wet weight^{-1}. *Taurine and carnosine excluded; †$P < 0·05$; ‡$P < 0·01$, §$P < 0·001$ (postoperative *versus* preoperative values, Student's *t* test for paired samples)

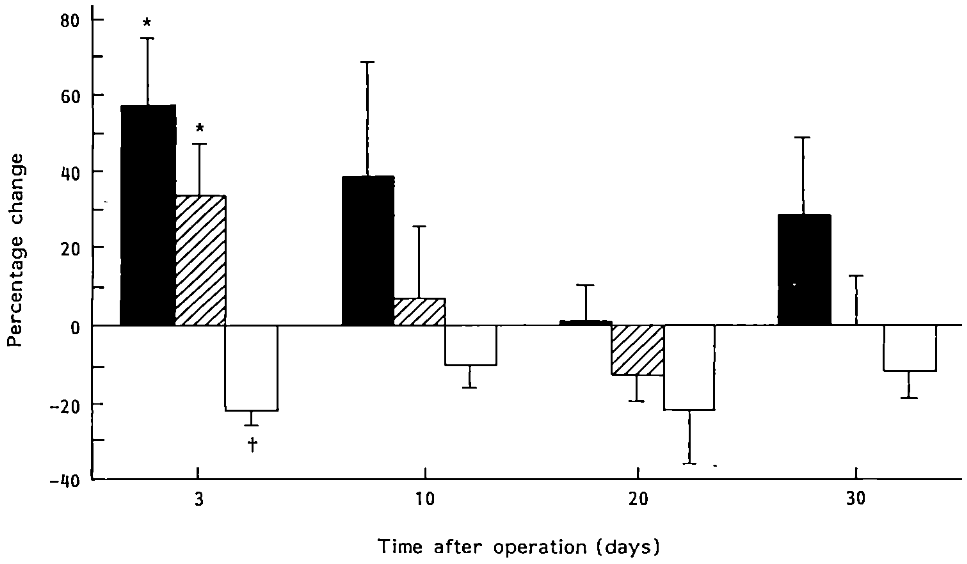

Figure 1 *Changes in the concentrations of aromatic amino acids* (■), *branched chain amino acids* (▨) *and total amino acids* (☐) *on the third, tenth, 20th and 30th day after elective surgery. Values are mean(s.e.m.) expressed as percentage changes from preoperative levels.* *$P < 0·05$; †$P < 0·01$ (*day 3* versus *preoperative values, Student's* t *test for paired samples*)

in muscle (*Table 2*) decreased on the third day after surgery by 22·2(3·8) per cent ($P < 0·01$), but returned to normal on day 10 after surgery (*Figure 1*). No significant change in the total concentration of essential amino acids or basic amino acids (lysine, histidine, arginine) was noted after operation. On the other hand, the concentration of BCAAs and aromatic amino acids (AAAs) increased on the third day after operation by 33·7(13·7) and 57·2(17·8) per cent, respectively ($P < 0·05$), but returned to the preoperative level by the tenth day after surgery (*Figure 1*). Among the individual amino acids, glutamine levels decreased on the third and tenth days after operation by 37·5(3·9) per cent ($P < 0·001$) and 20·0(5·9) per cent ($P < 0·05$), respectively, compared with preoperative values (*Figure 2*). On the 20th day after operation the concentration of glutamine was not significantly different from the basal level before surgery, but on the 30th day after surgery the concentration of free glutamine was still reduced by 22·4(9·0) per cent ($P < 0{\cdot}05$) compared with the preoperative value. Glutamate concentration was reduced on the third day following surgery by 34·9(6·4) per cent ($P < 0{\cdot}05$) but returned to the preoperative level on day 10 after surgery. There was a slow but steady decrease in the carnosine concentration which did not reach statistical significance until the 30th day after operation, when it was reduced by 32·7(9·6) per cent ($P < 0{\cdot}05$). The concentrations of isoleucine and phenylalanine increased on the third day after operation by 113·7(30·6) per cent ($P < 0{\cdot}01$) and 59·5(18·7) per cent ($P < 0{\cdot}05$), respectively, but returned to the preoperative level on day 10 after operation.

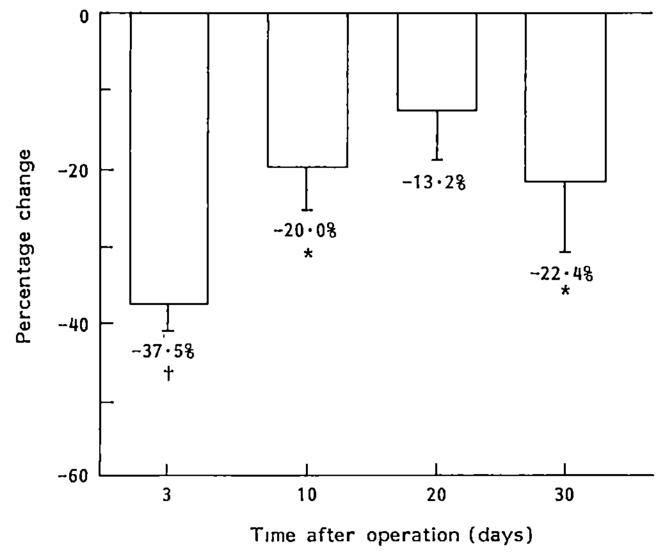

Figure 2 *Decrease in muscle glutamine concentration on the third, tenth, 20th and 30th day after elective surgery Values are mean(s e m.) expressed as percentage changes from preoperative levels.* *P < *0 05,* †P < *0 001 (postoperative* versus *preoperative values, Student's* t *test for paired samples)*

The total concentration of amino acids in plasma showed no significant change from the preoperative value (*Table 3*), whereas the sum of essential amino acids increased on the third day after operation by 30·9(8·6) per cent ($P < 0{\cdot}01$). The sum of AAAs increased on the third and tenth days following surgery by 32·4(9·3) per cent ($P < 0{\cdot}01$) and 24·0(4·2) per cent ($P < 0{\cdot}001$), respectively, compared with the value before operation. An increase was also noted in the total concentration of basic amino acids on the third and tenth days after operation by 22·4(9·1) per cent ($P < 0{\cdot}05$) and 23·3(9·6) per cent ($P < 0\ 05$), respectively, and the total concentration of BCAAs increased on the third day after operation by 27·8(8·0) per cent ($P < 0{\cdot}01$) compared with the preoperative value.

Discussion

Thirty days after elective surgical trauma the free amino acid pattern in skeletal muscle still had not been completely restored. After 1 month muscle glutamine was still decreased by 22·4(9·0) per cent compared with the preoperative value, demonstrating a very slow recovery. The pronounced drop in muscle glutamine levels 3–5 days after surgical trauma is reproduced in a large number of investigations[1,2,8–11]. This reduction does not occur immediately, but develops gradually during the 24–72 h after the surgical trauma[3]. The fall in muscle glutamine seems to be related to the surgical trauma and not to general anaesthesia, as it is also seen after accidental trauma without anaesthesia and also after spinal anaesthesia[12]. With persistent abdominal infection, sepsis or necrotizing

Table 3 *Concentration of free amino acids in plasma before elective abdominal surgery and on days 3, 10, 20 and 30 after operation*

Amino acid	Before operation	After operation Day 3	Day 10	Day 20	Day 30
Taurine	98(8)	81(4)	117(13)	99(9)	105(5)
Aspartate	11(2)	12(2)	13(2)	12(2)	10(1)
Threonine	147(12)	191(11)*	183(17)*	185(13)	179(19)*
Serine	150(18)	167(9)	158(14)	179(15)	153(14)
Asparagine	77(8)	96(19)	81(7)	93(6)*	74(8)
Glutamate plus glutamine	844(39)	800(26)	833(57)	883(43)	830(48)
Glycine	265(34)	289(19)	331(38)†	371(44)†	338(33)‡
Alanine	407(33)	469(32)	547(57)*	562(62)*	520(32)*
Valine	335(17)	381(17)	313(17)	314(21)	308(13)
Methionine	26(1)	43(3)†	36(3)†	35(3)	32(2)*
Isoleucine	78(9)	125(7)†	102(10)	103(10)	91(6)
Leucine	177(11)	236(12)†	182(15)	189(17)	166(8)
Tyrosine	60(5)	94(4)†	80(4)‡	82(10)	76(3)†
Phenylalanine	66(4)	89(6)*	80(3)*	75(4)	71(2)
Lysine	256(19)	334(17)*	322(21)*	307(20)	275(16)
Histidine	120(4)	109(4)*	106(6)	122(4)	107(5)
Tryptophan	63(2)	62(6)	72(4)*	72(5)	62(5)
Arginine	102(11)	129(11)	153(17)*	119(9)	120(12)
Sum of					
Aromatic amino acids	188(11)	245(12)†	232(9)‡	236(16)	208(6)
Branched chain amino acids	590(36)	742(32)†	597(39)	606(48)	566(24)
Basic amino acids	478(30)	572(24)*	581(41)*	548(29)	501(27)
Essential amino acids	1208(65)	1555(54)†	1369(71)	1387(91)	1261(46)
Total amino acids	3280(183)	3764(95)	3676(275)	3895(185)	3515(149)

Values are mean(s e m) expressed in μmol l^{-1}. *$P < 0{\cdot}05$, †$P < 0{\cdot}01$, ‡$P < 0{\cdot}001$ (postoperative *versus* preoperative values, Student's *t* test for paired samples) pancreatitis, the reduction becomes even more pronounced in several studies[9,13–15], although conflicting results have also been reported[16]. In these cases the reduction in muscle glutamine seems to be long-standing and a persistent low level is accompanied by a fatal outcome[14]. However, a slow trend towards restoration has been reported in patients with necrotizing pancreatitis having a favourable clinical course[15]. Among patients undergoing elective surgery, a normalization to preoperative values on day 20 after hip replacement has been reported[17]. The time course of the recovery after uncomplicated abdominal surgery has not been described previously. Here we see a low level on day 3 after operation which had partly returned to baseline values on days 10, 20 and 30. Although levels were not significantly different from the preoperative value on day 20, six of seven subjects showed a concentration lower than baseline at this time. Thus the pattern indicates that the large fall in the preoperative glutamine level of 37·5(3·9) per cent by day 3 had been reduced by half on the tenth day following surgery. However, after this point the return to normal seems to be very slow. Surgical trauma is often accompanied by starvation or semistarvation. In this study the patients received the routine nutritional treatment in hospital, thus establishing the natural course of the parameters studied.

Intravenous dextrose was given on the day of surgery and thereafter the oral intake was increased at will so as to be back to the preoperative level around the seventh day after operation[4]. The typical postoperative pattern of free amino acid levels in muscle on the third day after surgery is not influenced by conventional intravenous nutrition[18]. On the other hand, starvation for 5 days reproduces the pattern of muscle amino acids seen after trauma[19]. Upon refeeding, however, the prestarvation pattern was restored within 2 days. Such a quick recovery was not seen here, but that does not imply that nutritional factors should be disregarded. Although conventional total parenteral nutrition (TPN) is ineffective in preventing a substantial fall in muscle glutamine levels, when TPN is supplemented with glutamine this drop is prevented[8,11]. Glutamine is not included in conventional TPN regimens owing to its instability in aqueous solution. The glutamine content of ordinary food eaten by patients is approximately 7 per cent, while the glutamine content of the experimental amino acid solutions for intravenous use referred to above was 20–25 per cent. Obviously, an extra supply of glutamine may prevent the fall in muscle glutamine levels, but it is still unclear whether the restoration of an already low content of glutamine in muscle may be influenced by nutritional means.

Much interest has been focused recently on glutamine, which constitutes two-thirds of total free intracellular amino acids in muscle. Glutamine is constantly produced by muscle and a net release is seen even during meals and intravenous infusion of amino acids[20,21]. Following trauma the enhanced efflux of glutamine from muscle is accompanied by a low intracellular concentration of this amino acid[2,22]. Muscle protein synthesis declines following surgery irrespective of whether or not conventional TPN is given[23,24].

Addition of glutamine or α-ketoglutarate to postoperative TPN regimens abates this decline, however[8,25,26]. After cholecystectomy there is a weak but statistically significant correlation between the change in muscle glutamine concentration and the alteration of muscle polyribosome content which reflects protein synthesis[26]. In animals the correlation between muscle glutamine concentration and the rate of muscle protein synthesis is very strong[27,28]. When ribosome parameters were measured to estimate protein synthesis during a period of 30 days after surgery, a substantial drop was seen on days 3 and 10, with restoration being slow, if observed at all[4]. Thus there was total congruence between the changes in muscle glutamine and polyribosomes. However, immediately after elective surgery when the drop in muscle glutamine is barely detectable, the rate of muscle protein synthesis is lowered by more than 30 per cent[3,24]. At this point the relation between free glutamine and protein synthesis in muscle remains an open question.

Concomitant with the low glutamine level after operation, BCAAs and AAAs show elevated concentrations[2]. In this study these changes were seen on day 3 after operation, with a return to normal on day 10. Normally, glutamine is synthesized by transamination of α-ketoglutarate and glutamate from BCAAs, whose carbon skeletons are then oxidized in muscle[29]. It has been hypothesized that a relative shortage of α-ketoglutarate develops in muscle[26]. α-Ketoglutarate is a central substance in cellular energy metabolism, being part of the tricarboxylic acid (TCA) cycle. Entry of BCAAs into the TCA cycle may be limited when there is a relative shortage of TCA cycle intermediates such as α-ketoglutarate[26].

This may explain the apparent conflict between the high BCAA and AAA levels and the low glutamine concentration, considering that BCAAs are the major source for glutamine synthesis. Additional evidence favouring this hypothesis is the pattern of the development of high muscle levels of BCAAs after operation. Initially, the decline in muscle BCAA levels is paralleled by low levels in plasma[3]. At 24 h after operation, however, this decline is reversed into an increase. This undulating time course is consistent with the concept of increased glutamine production, eventually limited by a relative shortage of α-ketoglutarate, which also limits the oxidation of BCAAs in muscle.

In the plasma some alterations of amino acid concentrations were seen on day 3 after operation. On day 10, however, an elevation of phenylalanine persisted, consistent with earlier findings[30]. This reflects the difference in metabolism of BCAAs and phenylalanine; the latter is transported to the liver to be deaminated. The rationale for the long-standing elevation of the plasma phenylalanine level is unclear, but competition for transmembrane carriers of amino acids has been suggested[1]. A similar competition or down-regulation in the efficacy of the transmembrane carrier in muscle may be responsible for the very slow complete restoration of the muscle glutamine concentration[31].

In conclusion, a pilot study of the natural course after elective abdominal surgery revealed that the initial decrease in muscle glutamine still had not been fully restored after 30 days. Other aberrations regarded as part of the characteristic post-traumatic amino acid pattern on the third day after operation were restored 1 week later. The results constitute a baseline for future studies in which the impact of nutritional and pharmacological therapies will be evaluated beyond the immediate postoperative period.

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Randomized, controlled study evaluating effects of branched chain amino acids and alpha-ketoisocaproate on protein metabolism after surgery

The effect of nutritional supplementation with branched chain amino acids or the ketoacid α-ketoisocaproate on protein metabolism after surgery was studied in 24 patients with gastrointestinal cancer. They were randomized to receive one of three nutritional regimens. All patients received a balanced amino acid solution and group 1 ($n = 8$) *received no further supplements, group 2* ($n = 8$) *received supplementation with α-ketoisocaproate (17 g day*$^{-1}$*) and group 3* ($n = 8$) *received a branched chain solution including leucine, isoleucine and valine, corresponding to 3·3 g nitrogen day*$^{-1}$*. Plasma albumin, prealbumin, fibronectin and serum urea concentrations, nitrogen balance and 3-methylhistidine release from the leg and its excretion in the urine were measured. Albumin and prealbumin concentrations fell after surgery in all groups, and fibronectin levels fell in group 2* ($P < 0\cdot001$)*. In group 2 there was also a significant increase in serum urea concentration after operation* ($P < 0\cdot05$)*. Cumulative nitrogen balance after 3 days was −5·6 g (group 1), −3·8 g (group 2) and −1·7 g (group 3). The release of 3-methylhistidine (nmol 100 g*$^{-1}$ *min*$^{-1}$*) from the leg after operation, following an overnight fast, was −0·42 (group 1), −0·51 (group 2) and −0·66 (group 3). During infusion the release was −0·56, −0·99 and −0·81, respectively. A balanced amino acid solution with an adequate energy supply has an optimal nitrogen-sparing effect. Branched chain amino acids or α-ketoisocaproate did not improve nitrogen balance or reduce protein degradation.*

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Surgical trauma is followed by a catabolic state with an increase in resting energy expenditure and a net loss of body protein[1]. Most of the excreted nitrogen is derived from skeletal muscle protein by mobilization of amino acids for energy and visceral synthesis of proteins[2]. A negative nitrogen balance occurs immediately after surgery, with losses of up to 20 g nitrogen day^{-1}, despite adequate nutritional support[3]. To reduce net protein degradation, branched chain amino acids (BCAAs) have been given. These stimulate protein synthesis and reduce protein degradation *in vitro* in the liver and skeletal muscle[4,5]. Unlike leucine its α-keto analogue, α-ketoisocaproate, reduces the postoperative negative nitrogen balance when given in addition to a hypocaloric nutritional regimen[6]. Clinical studies have shown favourable[7,8] and unfavourable[9] results of BCAA-enriched nutritional regimens in the control of protein metabolism after operation.

This randomized, controlled study evaluated the effects of infusion of α-ketoisocaproate and BCAAs on protein metabolism in the first 3 days after major surgery. The results were compared with those from a control group who received conventional total parenteral nutrition (TPN).

Patients and methods

Twenty-four patients undergoing major abdominal surgery were studied (*Table 1*). Those with diabetes, cardiac failure or renal, hepatic or thyroid disease were excluded. The patients were randomized to one of three postoperative nutritional regimens. The study was approved by the local ethics committee.

Nutritional regimens

The TPN regimen was designed to provide 146 kJ (35 kcal) kg^{-1} 24 h^{-1} of non-protein calories as isocaloric parts of glucose and fat (Intralipid 20%; Kabi Pharmacia, Stockholm, Sweden). The different nutritional regimens were isonitrogenous and designed to provide 0·2 g nitrogen kg^{-1} 24 h^{-1}. The group receiving conventional TPN (group 1, $n = 8$) was given Vamin 14 (Kabi Pharmacia) containing 18·4 per cent BCAAs. Group 2 ($n = 8$) was given 60 mmol (17 g) α-ketoisocaproate in a balanced amino acid solution. Group 3 ($n = 8$) received an enriched solution containing 37 per cent BCAAs (7 g isoleucine, 14 g leucine and 9 g valine 1000 ml^{-1}) with a balanced amino acid solution. Electrolytes, trace elements and vitamins were added. No other nutrients were allowed. TPN was given for 16 h a day up to 78 h after operation.

Protocol

Patients were asked not to eat meat for the 2 days before admission. Blood samples were taken on the morning of operation, 72 h after operation in the morning (6 h after that day's infusion had stopped), and 78 h after operation while undergoing TPN. Urine was collected as 24-h specimens for 3 days beginning on the first day after operation.

Table 1 *Patient details of the three groups*

	Group 1 ($n = 8$)	Group 2 ($n = 8$)	Group 3 ($n = 8$)
Mean(s.e.m.) age (years)	61·4(4·6)	57·7(6·9)	55·4(8·3)
Sex ratio (M:F)	6:2	7:1	5:3
Mean(s.e.m.) weight (kg)	72·3(3·9)	74·5(3·9)	69·5(4·6)
Disease			
Benign	4	3	3
Malignant	4	5	5

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Biochemical variables

Serum concentrations of glucose, urea, creatinine, bilirubin and albumin were measured with an automatic flow analyser (SMAC; Technicon, Stockholm, Sweden). Prealbumin concentration was measured by electroimmunoassay[10] and fibronectin by immunochemical precipitation and laser nephelometry[11]. Samples of arterial blood for estimation of 3-hydroxybutyrate concentration were taken in duplicate and immediately precipitated using ice-cold perchloric acid. After centrifugation the protein-free extract was frozen at −80°C. Analyses were performed by microfluorometry as previously described[12].

Arteriovenous difference and net efflux of 3-methylhistidine

Arterial and venous blood samples were drawn simultaneously. The leg blood flow was measured by automatic mercury strain gauge plethysmography (Medimatic; Copenhagen, Denmark). Five measurements of leg blood flow were made at the maximal circumference of the calf immediately before and after blood sampling The mean blood flow of the ten measurements was calculated and multiplied by the arteriovenous difference. The uptake and the release of 3-methylhistidine was given in nmoles per 100 gram of tissue per minute, assuming the mean density of leg tissue to be 1·0 g ml^{-1} The method for analysing the concentration of 3-methylhistidine in plasma has previously been described[13].

Urine

The 24-h specimens of urine were analysed for creatinine, 3-methylhistidine and total nitrogen concentrations.

The total nitrogen concentration was measured by the micro-Kjeldahl method[14]; the non-urinary nitrogen losses were estimated to be 1·5 g day^{-1}. The daily and cumulative whole body nitrogen balance was calculated and corrected for the change in blood urea.

The concentration of 3-methylhistidine in urine was measured using an automated amino acid analyser (Kontron, Basel, Switzerland)[15].

Statistical analysis

The significance of differences between the means of the groups was assessed by variance analyses and Student's unpaired *t* test, and within the groups by Student's paired *t* test. $P < 0{\cdot}05$ was accepted as significant.

Table 2 *Serum glucose, urea, creatinine, bilirubin and plasma protein concentrations before and 72 h after major operation*

	Group 1		Group 2		Group 3	
	Before	After 72 h	Before	After 72 h	Before	After 72 h
Serum glucose (mmol l^{-1})	6·5(0·4)	8·8(1·2)	6·6(0·6)	9·5(1·5)	5·7(0·5)	9·8(1·7)
Serum urea (mmol l^{-1})	4·4(0·6)	4·9(0·5)	4·7(0·7)	8·9(1·5)*	4·3(0·2)	5·4(0·7)
Serum creatinine (μmol l^{-1})	87·9(6·5)	75·0(6·3)	90·0(4·2)	93·0(8·9)	100·8(5·2)	86·0(7·3)
Serum bilirubin (μmol l^{-1})	10·4(1·4)	10·5(1·2)	11·4(1·4)	15·6(4·8)	10·6(0·9)	13·5(0·9)
Plasma albumin (g l^{-1})	35·0(1·4)	27·0(1·5)†	37·1(0·7)	27·7(1·7)†	35·5(1·6)	29·3(2·0)*
Plasma prealbumin (g l^{-1})	0·22(0·02)	0·13(0·02)*	0·20(0·01)	0·10(0·01)‡	0·20(0·03)	0·11(0·01)*
Plasma fibronectin (%)	116(6·5)	96(18)	124(9·3)	65(4·4)‡	92(6·1)	75(6·8)

Values are mean(s.e.m.). *$P < 0{\cdot}05$; †$P < 0{\cdot}01$; ‡$P < 0{\cdot}001$ (before surgery *versus* after 72 h, Student's paired *t* test)

Table 3 *Arteriovenous difference and net efflux of blood flow from the leg for 3-methylhistidine and concentrations of 3-hydroxybutyrate in arterial blood before and 72 and 78 h after operation in patients receiving total parenteral nutrition*

	Group 1			Group 2			Group 3		
	Before	After 72 h	After 78 h	Before	After 72 h	After 78 h	Before	After 72h	After 78 h
Blood flow (ml 100 g tissue^{-1} min^{-1})	2·39(0·29)	1·91(0·15)	1·95(0·14)	1·99(0·22)	2·14(0·24)	2·72(0·25)	3·07(0·69)	2·59(0·37)	3·18(0·42)
3-Methylhistidine									
Arteriovenous difference (μmol l^{-1})	−0·23(0·03)	−0·24(0·06)	−0·29(0·06)	−0·22(0·03)	−0·21(0·05)	−0·38(0·07)	−0·20(0·04)	−0·23(0·05)	−0·23(0·05)
Net efflux (nmol 100 g tissue^{-1} min^{-1})	−0·54(0·10)	−0·42(0·09)	−0·56(0·11)	−0·42(0·07)	−0·51(0·17)	−0·99(0·19)*	−0·54(0·08)	−0·66(0·21)	−0·81(0·23)
3-Hydroxybutyrate (mmol l^{-1})	0·55(0·12)	0·02(0·00)	0·05(0·01)	0·51(0·12)	0·11(0·06)	0·20(0·09)	1·22(0·47)	0·04(0·01)	0·08(0·03)

Values are mean(s.e.m.) *$P < 0{\cdot}05$ (after 78 h *versus* before and 72 h after operation. Student's paired *t* test)

Table 4 *Daily and cumulative nitrogen balance and cumulative urinary 3-methylhistidine excretion on days 1, 2 and 3 after major operation*

	Group 1			Group 2			Group 3		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Nitrogen balance (g day^{-1})	−2·8(1·5)	−2·0(1·2)	−0·8(0·7)	−1·0(1·5)	−2·7(1·4)	−0·1(1·2)	−0·5(0·8)	−0·6(0·8)	−0·6(0·8)
Cumulative nitrogen balance (g on days 1–3)	−2·8(1·5)	−4·8(2·4)	−5·6(2·4)	−1·0(1·5)	−3·7(1·3)	−3·8(2·2)	−0·5(0·8)	−1·1(1·3)	−1·7(1·8)
Urinary 3-methylhistidine excretion (μmol mmol creatinine^{-1} day^{-1})	25·2(1·4)	25·1(1·7)	25·6(1·8)	27·8(2·3)	25·9(2·9)	34·3(11·1)	22·1(2·7)	23·9(2·2)	21·9(1·3)
Cumulative urinary 3-methylhistidine excretion (μmol mmol creatinine^{-1})	25·2(1·4)	50·3(3·8)	75·9(7·1)	27·8(2·3)	53·7(5·0)	88·0(14·8)	22·1(2·7)	46·0(4·2)	67·9(7·2)

Values are mean(s.e.m.)

Results

Biochemical variables (Table 2)

The serum glucose concentration did not increase significantly and there were no differences among the groups 72 h after operation. The serum urea concentration increased 72 h after surgery in group 2 by 89 per cent ($P < 0{\cdot}05$), but not in the other two groups.

The plasma albumin concentration fell significantly in all groups, but the values did not differ significantly at 72 h.

The plasma fibronectin concentration had fallen in all groups at 72 h, but significantly only in group 2 ($P < 0{\cdot}001$), the mean value being below the lower limit of the reference range for healthy subjects.

Arteriovenous differences and net efflux of 3-methylhistidine (Table 3)

All patients receiving TPN had a net efflux of 3-methylhistidine from the leg before and 72 and 78 h after operation. In group 2, the net efflux on the third day 78 h after operation was significantly increased compared with values obtained before and 72 h after operation. In groups 1 and 3 there were no significant changes in net efflux from the leg after operation and 78 h later.

Nitrogen balance (Table 4)

The daily and cumulative nitrogen balances were negative in all three groups, but only slightly so, and no differences were found between them.

Urinary excretion of 3-methylhistidine (Table 4)

To correct excretion of 3-methylhistidine for variations in muscle mass, it was related to urinary creatinine excretion. The mean daily and cumulative values for 3-methylhistidine were similar in all three groups and did not differ significantly.

Discussion

The metabolic response to trauma entails a net protein loss of up to 20 g nitrogen (equivalent to 500–600 g wet skeletal muscle)[1,3]. The nitrogen losses are the result of increased protein degradation and, although protein synthesis is stimulated, the net effect is negative[16]. Nutritional support reduces negative nitrogen balance[16], and adequate calories to keep the patient in energy balance will keep nitrogen loss to a minimum[17] Giving nitrogen in the form of a balanced amino acid solution reduces, but does not abolish, negative nitrogen balance. Nitrogen was retained (up to $0{\cdot}2\,\mathrm{g\,kg^{-1}\,24\,h^{-1}}$) during the first week after trauma[18]. Other nitrogen-saving techniques, such as using epidural analgesia, have been proposed but are difficult to apply in those with extensive trauma[19]

BCAAs, particularly leucine, reduce protein breakdown and stimulate protein synthesis at physiological concentrations *in vitro* in skeletal muscle and liver[20,21]. Their effects *in vivo* are controversial. Decreased protein degradation is not an effect of leucine alone but requires its transamination to ketoleucine. Ketoleucine has been shown to spare nitrogen in obese fasting subjects[22]. In a study of surgical patients, ketoleucine caused significant ketosis, and ketosis may inhibit protein degradation[6] In this study ketoleucine was given to assess its effect on protein degradation in muscle in three comparable groups of patients

Albumin and prealbumin concentrations decreased after operation and there was a decline in fibronectin in group 2. Leucine and ketoleucine may stimulate hepatic protein synthesis[6,21] and hepatic synthesis of acute phase proteins in critically ill and septic rats was stimulated by an amino acid solution enriched with 45 per cent BCAAs[21]. In this study the levels of plasma proteins with short half-lives, prealbumin (48 h) and fibronectin (8 h) both declined, more in group 2 than the other groups.

The whole body nitrogen balance was not affected by either BCAAs or ketoleucine. In a study of patients after operation, Sapir *et al* [6] showed that ketoleucine plus glucose improved nitrogen balance and suppressed proteolysis, which was indicated by reduced urinary 3-methylhistidine excretion Leucine did not seem to have the same effect The increase in urea concentrations in the keto group at 72 h in the present study probably represented impaired breakdown of the ketoleucine solution

3-Methylhistidine is found exclusively in actin and myosin and is released during proteolysis, after which it is neither reused for protein synthesis nor catabolized further. In the present study, excretion of 3-methylhistidine in urine was increased in all three groups[16], which indicates that myofibrillar proteolysis is not influenced by either BCAAs or balanced amino acids enriched with ketoleucine It has been shown that 3-methylhistidine excretion is not influenced by the supply of balanced amino acids[16], but is related to the degree of injury and is mostly of skeletal muscle origin[23]. The significantly improved nitrogen balance in patients after operation that was reported by Sapir *et al.*[6] was attributed to a reduced excretion of 3-methylhistidine. The arteriovenous difference in 3-methylhistidine excretion and the net release from one leg were increased during TPN in group 2, indicating that ketoleucine had, on the contrary, a proteolytic effect In the group receiving only a balanced amino acid solution (group 1) there was no such effect Provided that adequate balanced nutritional support is given, supplementary ketoleucine and BCAAs do not seem to have any beneficial effects on protein metabolism.

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Dormant liver metastases: an experimental study

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Experimental work was undertaken to evaluate whether intrahepatic recurrences, observed after resection of colorectal liver metastases in humans, could be due to the activation of dormant cancer cells already present within the liver at liver resection. About 250 cell aggregates (DHDK12 colon carcinoma cell line) were injected into the portal vein of 70 BD IX rats. Eight weeks later, 43 rats with no apparent liver metastases were divided randomly into three groups: group 1 ($n = 15$) *served as control; group 2* ($n = 15$) *were given cyclosporin A (10 mg kg body-weight*$^{-1}$ *day*$^{-1}$*) for 28 days; and group 3* ($n = 13$) *underwent a 70 per cent hepatectomy. Twelve weeks after the injection of cells, when the animals were killed, 20 per cent of rats in group 1 had liver metastases, 80 per cent in group 2* ($P < 0{\cdot}01$) *and 62 per cent in group 3* ($P < 0{\cdot}05$)*. Undetectable liver micrometastases may have been present at 8 weeks and had not developed until stimulation by cyclosporin A-induced immunosuppression or by liver regeneration after hepatectomy. A similar mechanism may occur clinically and explain some of the recurrences observed after resection of liver metastases.*

The prognosis for patients with colorectal cancer has not improved in recent years and the survival rate at 5 years remains about 40 per cent after surgical excision[1]. Liver metastases are discovered in up to one-quarter of patients at the time of excision of primary colon cancer[2], and appear later in another 30–40 per cent of patients[3–6]. Once liver metastases have occurred, surgical excision remains the best available method to prolong survival in some patients[3,5,7].

After surgical resection of colorectal liver metastases, intrahepatic recurrences occur in 30–40 per cent of patients, often very soon after surgery[3]. There are three likely explanations for these recurrences. First, multifocal liver metastases may not have been recognized; although new imaging procedures (ultrasonography, preoperative computed tomography and intraoperative ultrasonography)[8–10] can detect liver metastases of 0·5 cm in diameter, the rate of recurrence after apparently curative liver resection remains unchanged. Second, extrahepatic metastases (peritoneal, lymph nodes, pulmonary) may have been missed; macroscopic extrahepatic metastases are detected by careful preoperative and peroperative assessment before resection for liver metastases, but micrometastases can be missed and could explain some intrahepatic recurrences. A similar situation has been described after total hepatectomy and liver transplantation for liver metastases in humans[11,12]. Third, there may have been activation of cancer cells already present within the liver remnant but which remained dormant until liver resection.

This work was undertaken to test this last hypothesis in an experimental model of colorectal liver metastases induced by intraportal injection of cancer cells.

Materials and methods

Seventy syngeneic male BD IX rats (CNRS, Orléans, France) were used. The animals were given free access to standard laboratory chow and water throughout the experiment. The DHDK12 cell line is an established transplantable carcinoma cell line originating from a 1,2-dimethylhydralazine-induced colon adenocarcinoma in BD IX rats[13,14]. Cells were maintained in monolayer culture as previously described[15] Approximately 250 aggregates (150–200 μm in diameter), obtained from the incubation of 500×10^3 cells on a giratory shaker for 48 h[15], were injected into the portal vein through a minicatheter (butterfly no. 21; Abbott, Rungis, France). The site of injection was covered with a haemostatic sponge.

Eight weeks later, at laparotomy, rats with macroscopic liver metastases were excluded from the study ($n = 22$). Five rats were not evaluable All the others with no apparent metastases ($n = 43$) were divided randomly into three groups: group 1 were the control animals ($n = 15$); group 2 ($n = 15$) were given cyclosporin A (Sandoz, Rueil, France) in olive oil at a dose of 10 mg kg body-weight^{-1} daily by subcutaneous injection for 4 weeks, group 3 ($n = 13$) underwent a 70 per cent hepatectomy. The rats were killed 12 weeks after cell injection. No information about group identity was given to the examiner before the autopsy was completed. The peritoneal cavity and the thorax were examined carefully; the liver and any suspected visceral or peritoneal metastases were examined histopathologically.

Fisher's exact test with Yates' correction was used to compare the numbers of rats with liver metastases in the different groups.

Results

A total of 65 rats were evaluable: two early postoperative deaths were due to bleeding at the puncture site of the portal vein. Three animals died during the experiment and could not be evaluated accurately (one rat in group 2 and two rats in group 3). In all three groups, no macroscopic liver metastases were observed at 8 weeks after cell injection.

At sacrifice, in group 1, liver metastases confirmed by pathological examination were observed in three rats (20 per cent). In group 2, at sacrifice, metastases were observed in 12 rats (80 per cent). In one of these, lung metastases were found. The number of rats with liver metastases was significantly higher in group 2 than in group 1 ($P < 0{\cdot}01$). In group 3, at sacrifice, metastases were observed in eight rats (62 per cent). The number of animals with liver metastases was significantly higher in group 3 than in group 1 ($P < 0{\cdot}05$) (*Table 1*).

Table 1 *Liver metastases 12 weeks after cell injection*

Time after cell injection	Control group ($n = 15$)	Cyclosporin A group ($n = 15$)	Hepatectomy group ($n = 13$)
8 weeks	0	0	0
12 weeks	3	12*	8†

*$P < 0{\cdot}01$ (cyclosporin A *versus* control); †$P < 0{\cdot}05$ (hepatectomy *versus* control) (both Fisher's exact test)

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Discussion

This experimental model demonstrates that macroscopic liver metastases can develop 12 weeks after the intraportal injection of cancer cells in rats with no apparent metastases observed after a delay of 8 weeks[15]. The hypothesis is that undetectable liver micrometastases were present at 8 weeks, and were stimulated by cyclosporin A-induced immunosuppression and liver resection. These factors are known to stimulate tumour growth in other experimental models of malignancy[16–18]. After supposedly curative liver resection for liver metastases in humans, immunodepression, induced by laparotomy, and liver regeneration after hepatectomy could explain the stimulation of the 'dormant cells' and consequently early multifocal recurrence in the liver remnant.

In this study, 8 weeks after cell injection no macroscopic liver metastases were observed at laparotomy in 43 rats. In rats, some procedures have been proposed for the early detection of occult liver metastases: the hepatic perfusion index (decreased portal venous inflow)[19] and computed tomography[20]. Liver examination during laparotomy remains the best method (in rats) for early diagnosis of metastases, because the great majority develop superficially under Glisson's capsule[21,22]. The possible presence of undetectable liver micrometastases in this model at 8 weeks is similar to the clinical situation where peroperative liver examination and intraoperative ultrasonography may miss deep liver metastases with a diameter less than 0·5 cm[23].

Cyclosporin A dramatically increased the number of liver metastases, even though it was administered more than 8 weeks after cell injection. The immunosuppression induced by cyclosporin A promotes metastatic dissemination in several experimental tumours in the rat[16,22] When given at the time of cancer cell injection, cyclosporin A significantly increased the number of liver metastases induced by intraportal injection of cell aggregates[15,24], probably by reduction of the host cell infiltration (i.e. T lymphocytes and natural killer cells) which surrounded experimental liver metastases[15,25]. In this study, the stimulation of metastatic growth by cyclosporin A could be explained by the reduction in host cell infiltration around the undetectable liver micrometastases.

After partial liver resection, the regenerating liver releases growth factors which promote hepatic mitotic activity[18]. These factors have been shown, in most of the experimental studies, to increase the growth rate of several experimental tumours after partial hepatectomy[17,18,26,27]. Some have recently reported regression of tumours, or even disappearance, after partial hepatectomy in rats[28,29]. A 70 per cent hepatectomy performed in the rat in the 24 h before or after the intraportal injection of tumours cells promoted the development of liver metastases, the greater effect occurred when the resection was performed 5 min after the inoculation of the cancer cells[17]. In the present study, the growth of liver metastases was stimulated even though 8 weeks had elapsed between cell injection and hepatectomy. The mechanism of this late effect remains unclear.

Other factors have been shown to modulate the growth of experimental liver metastases: Kupffer cell inhibition[30,31], splenectomy[32] and repeated surgical procedures[26]. The operative period is critical for the development of metastases, owing to profound immunodepression in animals[33,34] and humans[35,36].

The theory of dormant cells was first introduced by Fisher and Fisher in 1959[37]. These cells may continue to survive indefinitely in a dormant state Some studies in humans have suggested the existence of two different tumour cell populations at the site of secondary tumour growth within the liver[38,39]: tumour cells growing to form metastases and tumour cells which appear morphologically to be in a resting non-proliferating state. When a small number of cells was injected intraportally in rats, no tumour was apparent 5 months later. When the rats were subjected to repeated laparotomies at 7-day intervals, 100 per cent developed a tumour 3 months after injection of the cells[26]. The effect on the dormant cells of hepatectomy and immunosuppression had not been demonstrated previously in experimental studies. These findings support the existence of dormant cells in the liver, which remain dormant and are not destroyed by the host. Dormant cells may begin to proliferate with liver regeneration after hepatectomy or when immunosuppression is induced by cyclosporin A and repeated surgical procedures

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Announcement

International Hepato-Biliary-Pancreatic Association Frank Glenn Travelling Fellowship 1992

The International Hepato-Biliary-Pancreatic Association invites applications for the above travelling Fellowship. A stipend of SFr 5000 is available to subsidize a young investigator in the field of hepatobiliary and pancreatic disorders. The applicant must be sponsored by a member of the Association. The stipend may be used to support a laboratory project and/or to subsidize travel expenses which are deemed appropriate to the field of investigation. Applicants must be under 40 years of age and should have an established record of at least one or several papers concerning liver, biliary or pancreatic disease.

Applications should be made in writing and should include the following:

1. a copy of the applicant's curriculum vitae;
2. a summary of 1–2 pages of a research protocol describing how the stipend is to be used;
3. a letter of nomination from a member of the IHBP Association or your Department Chairman.

Applications should be sent to: Dr Haile T. Debas, University of California, San Francisco, Department of Surgery, San Francisco, CA 94143-0104, USA by 30 April 1992. Telephone· (415) 476-1236. Facsimile: (415) 476-1734.

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Partial hepatic resection under intermittent hepatic inflow occlusion in patients with chronic liver disease

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A partial hepatic resection was performed in 13 patients with chronic liver disease using intermittent hepatic inflow occlusion. Eleven patients had liver cirrhosis and two had chronic hepatitis. Seven patients were classified as Child's grade A and six as Child's grade B before operation. Dissection of the hepatic parenchyma was performed during intermittent inflow occlusion. The time of clamping and declamping was 10–20 min and 5–8 min, respectively. Postoperative data on liver function showed recovery to preoperative levels by about 10 days after operation. There were no life-threatening complications. These results indicate that intermittent hepatic inflow occlusion can be achieved easily and safely to allow non-anatomical resection in patients with chronic liver disease.

The accepted and standardized resectional procedures in liver surgery have been a lobar or segmental resection. Resection in those with chronic liver disease, particularly cirrhosis, has been considered dangerous because of poor regeneration of the residual liver. Non-anatomical resection may be advocated to: (1) leave as much of a liver remnant as possible; (2) minimize intraoperative blood loss; and (3) shorten the liver ischaemic time.

The Pringle manoeuvre[1] reduces blood loss but the ischaemic time must be monitored, particularly in patients with chronic liver disease. The best method for liver resection would be surgery performed under intermittent hepatic inflow occlusion. This study investigated the postoperative damage following partial hepatic resection in patients with chronic liver disease using intermittent hepatic inflow occlusion. This was not a comparative study.

Patients and methods

During the past 2 years partial resection of the liver of less than one lobe was carried out using intermittent hepatic inflow occlusion in 13 patients with chronic liver disease. There were 11 men and two women with a mean age of 60 (range 49–70) years. Eleven patients had hepatocellular carcinoma, one had intrahepatic cholangiocarcinoma and one had a regenerating liver nodule. Eleven patients had cirrhosis and two had chronic hepatitis. Seven patients were classified as Child's grade A and six as Child's grade B before operation[2]. Results of preoperative liver function tests are shown in *Table 1*

The eight segments of the liver are as described by Couinaud[3].

Operative procedures

After mobilization of the liver, cholecystectomy and intraoperative ultrasonography were performed. The main hepatic pedicle was encircled with tape, as were the right and left branches of the inflow vessels. An ATOM (polyvinyl chloride, ATOM Medical, Tokyo, Japan) tube of 2·75 mm diameter was used for the snares. For hemihepatic inflow occlusion a smaller tube was used (2·0 or 2·35 mm in diameter).

When the tumour was located in the posterior segment of the right lobe (segments VI and VII) or the left lateral segment of the left lobe (II and III), hepatic resection was carried out by clamping the right or left branch of the inflow vessels When the tumour was located in the anterior segment of the right lobe (segments V and VIII) or the medial segment of the left lobe (IV), an occlusion of the total hepatic pedicle was sometimes needed because these regions receive blood from the opposite lobe The time of clamping and declamping was usually 10–20 min and 5–8 min, respectively, depending on the adequacy of preoperative liver function. During clamping, dissection of the liver was carried out using an ultrasonic surgical aspirator. Haemostasis was achieved with electrocautery. Haemostatic agents such as Avitene (Alcon, Humacao, Puerto Rico) or Oxycel (Becton–Dickinson, New Jersey, USA) cotton were used with suture ligation of the bleeding vessels during declamping The tumour-free margin was examined repeatedly using intraoperative ultrasonography. Clamping and declamping were repeated until the liver lesion had been completely resected

Table 1 *Preoperative liver function of patients with chronic liver disease undergoing hepatic resection*

	Liver cirrhosis ($n = 11$)	Chronic hepatitis ($n = 2$)
Child's grade		
A	5	2
B	6	0
Blood biochemistry		
Albumin (g/dl)	3·5(0·4)	3·9(0·1)
Bilirubin (mg/dl)	0·7(0·2)	0·6(0·0)
SGOT (units/l)	49(19)	48(18)
SGPT (units/l)	54(25)	72(23)

Values are mean(s.d.). SGOT, serum glutamic oxaloacetic transaminase (normal range 11–37 units/l), SGPT, serum glutamic pyruvic transaminase (normal range 7–30 units/l)

Results

Patient details are shown in *Table 2*. All patients had cirrhosis except numbers 1 and 6 Two patients (numbers 3 and 7) underwent a right hepatic lobectomy leaving a small volume of segment VIII. Other patients underwent a partial hepatectomy of less than one segment or two subsegments. One patient (number 1) had a small liver cancer of 3·5 cm in diameter situated in the bifurcation between the anterior and posterior branches of the right portal vein; this patient underwent a partial hepatic resection. Details of the occlusion times for each operation are shown in *Table 2*. Estimated blood loss during surgery ranged from 150 to 2700 ml (mean(s.d.) 1153(784) ml). Patient number 10 (2700 ml loss) underwent resection in two different regions (segments III and VII) and had undergone a gastrectomy. Mean(s.d.) operative time was 4·8(1·2) h in patients with cirrhosis and 4·6(1·9) h in those with chronic hepatitis. No instances of haemorrhagic shock occurred.

One patient (number 1) had a postoperative intraperitoneal abscess, and another (patient number 5) had a right pleural effusion which required pleural paracentesis. Two patients (numbers 7 and 12) suffered right ulnar nerve palsy after

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Table 2 *Details of patients undergoing hepatic resection*

Patient no.	Age (years)	Child's grade	Liver tumour	Tumour		Type of resection	Type of occlusion	Duration of occlusion time (min × frequency)	Revascularization time (min)	Intraoperative bleeding (ml)
				Localization (segment)	Diameter (cm)					
1	54	A	HCC	V	3·5	Partial	Total Right	10 × 4 10 × 3	5	730
2	55	B	HCC	V	3·5	Partial	Total Right	10 × 2 10 × 2	5	220
3	49	A	CC Haemangioma	V VIII	3·0 2·0	Right lobectomy	Total } Right }	10 × 4	5	2200
4	59	B	RN	VIII	2·0	Partial	Total Right	15 × 1 17 × 1	5	490
5	67	B	HCC	VIII	4·0	Partial	Total Right	10 × 2 15 × 2	5	1700
6	56	A	HCC	VIII	3·0	Partial	Total	15 × 3	5	150
7	68	A	HCC	V VII	1·5 1·5	Right lobectomy	Total Right	10 × 5 10 × 2	5	1700
8	58	A	HCC	VI	10·0	Partial	Total	20 × 2	8	1650
9	59	B	HCC	VIII	2·2	Partial	Total	10 × 2	5	600
10	63	B	HCC	III VII	2·0 3·5	Partial Partial	Total	10 × 5	5	2700
11	70	A	HCC	IV	4·0	Partial	Total Left	10 × 1 10 × 2	5	700
12	60	A	HCC	VII	3·5	Partial	Total } Right }	10 × 2	5	950
13	56	B	HCC	VI	1·4	Partial	Total } Right }	20 × 8	5	1200

HCC, hepatocellular carcinoma; CC, cholangiocarcinoma; RN, regenerating nodule

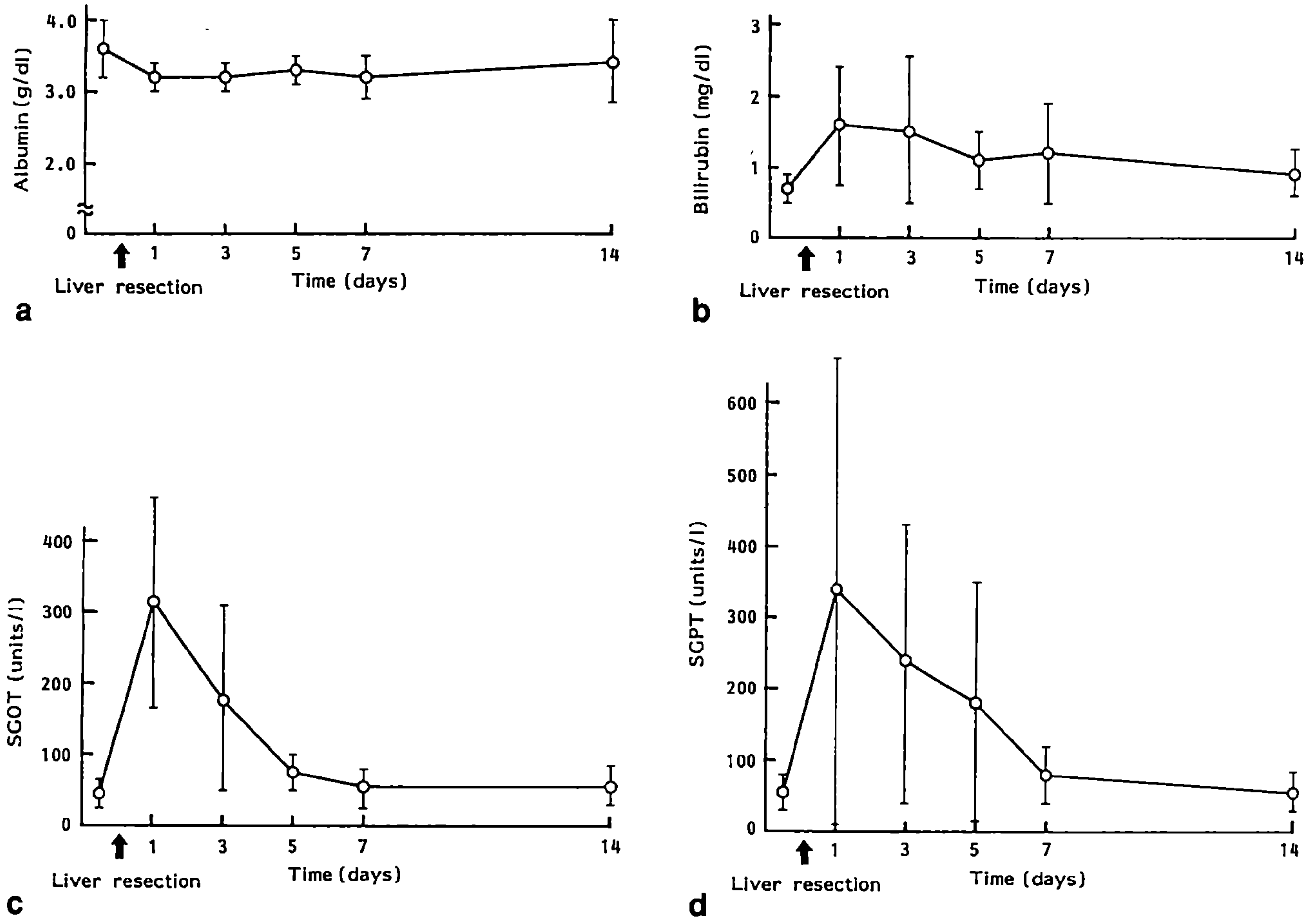

Figure 1 *Serial changes in* **a** *serum albumin level,* **b** *serum concentrations of total bilirubin,* **c** *serum activities of glutamic oxaloacetic transaminase (SGOT; normal range 11–37 units/l) and* **d** *serum activities of glutamic pyruvic transaminase (SGPT, normal range 7–30 units/l) after hepatic resection. Values are mean(s.d.)*

operation. There were no complications relating to the liver and no deaths related to surgery. The serial changes in the levels of albumin, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) of the patients are shown in *Figure 1*. Most parameters attained the preoperative levels by about 10 days after operation

Discussion

Recently liver resection has become safer and more widely practised, sometimes even without blood transfusion[4]. Bleeding must be kept to a minimum because it often leads to postoperative hepatic failure, particularly in those with cirrhosis[5]. Various methods have been described to reduce bleeding[6–9] but the total ischaemic time of the liver remnant must be kept to a minimum Delva *et al.*[6] reported that vascular occlusion was well tolerated (up to 60 min) in a normal liver. Makuuchi *et al.*[7] reported occlusion of the inflow vessels for up to 30 min using hemihepatic vascular occlusion in a cirrhotic liver. Ten to 20 min of ischaemia may be considered safe and there is a direct correlation between the levels of tissue adenosine triphosphate and the status of the hepatic blood supply[10].

It takes longer to perform hepatectomy under intermittent inflow occlusion but this may save the cirrhotic liver remnant by allowing a shorter overall ischaemic time. In the bloodless operative field which can be obtained during intermittent inflow occlusion, the surgeon can perform hepatic resection much more safely and easily by accurately confirming and managing the intrahepatic vessels. A reduced blood loss may be obtained during hepatic resection, particularly when dissecting the upper parts of the liver, if respiration is controlled to decrease the intrathoracic pressure and thereby the hepatic venous backflow.

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Polypoid lesions of the gallbladder: diagnosis and indications for surgery

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One hundred and eighty-two patients with an ultrasonographic and/or pathological diagnosis of polypoid lesions of the gallbladder (PLG) were reviewed to determine the reliability of ultrasonography in the diagnosis of PLG and the indications for operation in this disease. Of the 182 patients operated on, PLG were demonstrated by the gross appearance of the resected gallbladder in 172. Histologically benign lesions were present in 159 gallbladders and malignant lesions in 13. Cholesterol polyps accounted for most benign PLG. The sensitivity of ultrasonography in detecting PLG was 90·1 per cent, significantly higher than that of oral cholecystography, computed tomography or endoscopic retrograde cholangiopancreatography ($P < 0\cdot 01$). *The specificity of ultrasonography in the diagnosis of PLG was 93·9 per cent. Therefore, ultrasonography is a highly sensitive method for investigating PLG, and the preoperative diagnosis of PLG in this unit has now become entirely dependent on this technique. The size and number of PLG, the presence of gallstones and the patient's age all correlate with the nature of PLG, and these features are helpful in differentiating malignant from benign lesions before operation. Surgical treatment is indicated when PLG exceed 1·0 cm in diameter, when PLG are single in number, when PLG are associated with gallstones, when patients with PLG are over the age of 50 years, or when clinical symptoms of PLG are apparent.*

Polypoid lesions of the gallbladder (PLG) refer to any elevated lesions of the gallbladder[1,2]. The terminology and classification of these lesions remained ambiguous until 1970 when Christensen and Ishak[1] proposed a simplified classification on the basis of 180 benign tumours of the gallbladder. PLG can be divided into benign and malignant lesions. The benign PLG fall mainly into true tumours and pseudotumours of the gallbladder. The former can be further divided into the more common epithelial tumours (such as adenomas) and the rarer mesodermal tumours (such as leiomyomas and lipomas). Pseudotumours may be polyps, hyperplasia, heterotopia and so on[1,2]. PLG are now increasingly detected by ultrasonography Nevertheless, the nature of PLG is difficult to define before operation, and the indications for operative intervention in this condition remain controversial[2–4].

The present study reviewed the clinicopathological findings in 182 patients with PLG. Special attention was directed to determining the reliability of ultrasonography in diagnosing PLG by analysing the relative accuracy of ultrasonography, oral cholecystography, computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) in patients with PLG, and to identifying indications for operation by comparing the characteristics of benign and malignant lesions.

Patients and methods

From June 1982 to December 1990, 182 patients with an ultrasonographic and/or pathological diagnosis of PLG were registered and operated on at this hospital Preoperative ultrasonography was performed in all patients, oral cholecystography in 37, CT in eight, and ERCP in two Preoperative investigations were compared with operative findings. Aloka SSD60B (Aloka, Tokyo, Japan), Hitachi EUB-22 (Hitachi Medical, Tokyo, Japan), Aloka 210F, Aloka SSD630 and Hitachi EUB-40 scanners with a 3·0 or 3·5 MHz transducer were used successively The patients were scanned in the supine and lateral recumbent positions after fasting

Statistical analysis was performed using Student's unpaired t test and the χ^2 test. A P value $<0\cdot 05$ was considered statistically significant.

Results

Polyps were seen on macroscopic examination in 172 of 182 patients with a diagnosis of PLG. There were 93 men and 79 women (ratio (M:F) 1·18:1) with a mean age of 44·3 (range 15–76) years. Of the 172 patients, 140 (81·4 per cent) fell into the third, fourth and fifth decades of life. Twenty-eight (16·3 per cent) were asymptomatic and their PLG were detected incidentally on ultrasonography. However, the other 144 (83·7 per cent) complained of right upper quadrant or epigastric discomfort such as colic or dull pain, indigestion and distension, which led to ultrasonographic examination. Tenderness in the right upper quadrant was present in 55 patients (32·0 per cent)

Histological types of PLG in the 172 patients are listed in *Table 1* according to the classification of Christensen and Ishak[1]; 159 (92·4 per cent) were benign and 13 (7·6 per cent) were malignant Cholesterol polyps accounted for 108 of the 159 benign lesions (67·9 per cent). An inflammatory polyp was found in 12 patients, benign adenoma in ten, and adenomatous hyperplasia in eight.

The accuracy of ultrasonography, oral cholecystography, CT and ERCP in the diagnosis of PLG is shown in *Table 2*. Of the 172 patients with a macroscopic diagnosis of PLG, the preoperative diagnosis of PLG was correctly made by ultrasonography in 155, but in the remaining 17 PLG were diagnosed only by the gross appearance of the resected gallbladder and the postoperative pathological findings. Therefore the sensitivity of ultrasonography in the detection of PLG was 90·1 per cent (155 of 172). In contrast, the sensitivities of oral cholecystography, CT and ERCP were 24 per cent (nine of 37), 62 per cent (five of eight) and zero (neither of two), respectively ($P < 0\cdot 01$). In the 17 patients whose PLG were not detected by ultrasonography, 16 were associated with

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Table 1 *Pathological diagnosis in 172 cases of polypoid lesions of the gallbladder seen on macroscopic examination of the gallbladder*

Histological type	No of cases
Benign lesions ($n = 159$)	
True tumours	
Adenoma	
Papillary	2 (1·2)
Non-papillary	8 (4·7)*
Leiomyoma	1 (0·6)
Pseudotumours	
Polyp	
Cholesterol	108 (62·8)
Inflammatory	12 (7·0)
Hyperplasia	
Adenomatous	8 (4·7)
Adenomyomatous (adenomyoma)	4 (2·3)
Miscellaneous	
Chronic lymphadenitis in the gallbladder wall	2 (1·2)
Small haematoma in the gallbladder wall	1 (0·6)
Granuloma	
Cholesterol	1 (0·6)
Inflammatory	1 (0·6)
Cicatricial hyperplasia	1 (0·6)
Chronic cholecystitis	10 (5·8)
Malignant lesions ($n = 13$)	
Adenoma with malignancy	
Papillary	2 (1·2)
Non-papillary	2 (1·2)
Adenocarcinoma	
Papillary	2 (1·2)
Moderately differentiated	4 (2·3)
Poorly differentiated	2 (1·2)
Metastatic clear cell carcinoma	1 (0·6)
Total	172

Values in parentheses are percentages *One adenoma was associated with atypical hyperplasia

Table 2 *Accuracy of preoperative investigation in 182 patients with polypoid lesions of the gallbladder (PLG) diagnosed by ultrasonography and/or pathological examination*

Preoperative investigation	Total no. of patients	Preoperative diagnosis of PLG: Present	Preoperative diagnosis of PLG: Absent†
Ultrasonography	182	165*	17
Oral cholecystography	37	9	28
Computed tomography	8	5	3
Endoscopic retrograde cholangiopancreatography	2	0	2

*Includes ten false positive results, †final diagnosis was PLG in all cases

gallbladder stones. The difficulty of making a diagnosis of PLG in the presence of gallstones is shown by the observation that in 125 cases without gallstones PLG were detected correctly by ultrasonography in 124 (99·2 per cent) but not in one case where the gallbladder was filled with bile sludge. In contrast, in the other 47 cases with cholecystlithiasis, gallstones masked the presence of PLG in 16 and only 31 were correctly diagnosed before operation by ultrasonography ($P < 0·01$).

As shown in *Table 2*, a preoperative diagnosis of PLG was made by ultrasonography in 165 of the 182 patients This was confirmed in 155 (93·9 per cent) with ten false positives who had chronic cholecystitis Masses of multilobular soft yellow tissue were floating free in the gallbladder bile in three of these ten patients, and were diagnosed during operation as cholesterol polyps, but were not demonstrated on postoperative pathological examination. In another gallbladder multiple small gallstones were mistakenly diagnosed as PLG by preoperative ultrasonography

Table 3 *Differences in some features in benign and malignant polypoid lesions of the gallbladder (PLG) in 172 patients diagnosed by gross and microscopic examination*

	Total no of cases	PLG: Benign	PLG: Malignant	*P*
Age (years)				
<50	116	115 (99)	1 (1)	<0·01
≥50	56	44 (79)	12 (21)	
Sex				
M	93	88 (95)	5 (5)	n s
F	79	71 (90)	8 (10)	
Symptoms				
Yes	144	132 (92)	12 (8)	n s
No	28	27 (96)	1 (4)	
Blood group				
A	53	48 (91)	5 (9)	n s
B	43	40 (93)	3 (7)	
O	64	60 (94)	4 (6)	
AB	12	11 (92)	1 (8)	
Size of PLG (cm)*				
<1·0	138	138 (100)	0 (0)	<0·01
1·0–1·4	18	16 (89)	2 (11)	
≥1·5	16	5 (31)	11 (69)	
No. of PLG				
Single	86	73 (85)	13 (15)	<0·01
Multiple	86	86 (100)	0 (0)	
Gallstones				
Yes	47	40 (85)	7 (15)	<0·05
No	125	119 (95)	6 (5)	

Values in parentheses are percentages. *Greatest dimension, n.s , not significant

The patients' sex, symptoms and blood group did not correlate with the pathological type of PLG (*Table 3*). However, the mean(s.d.) age of 13 patients with malignant PLG at 59·6(12·7) years was significantly higher than that of 43·1(11·0) years in 159 cases with benign PLG ($P < 0·01$). Malignant lesions were found in 12 (21 per cent) of 56 cases aged 50 years or more Conversely, benign lesions were found in 115 (99·1 per cent) of 116 cases under 50 years of age ($P < 0·01$)

All of 138 PLG <1·0 cm in diameter were benign, but malignant lesions were found in two of 18 PLG between 1·0 and 1·4 cm in diameter. Eleven malignant lesions were detected in 16 PLG ≥1·5 cm in diameter ($P < 0·01$).

All of the 13 malignant PLG were solitary lesions. Malignant lesions were found in 13 (15 per cent) of 86 single PLG. In contrast, none of the 86 patients with multiple PLG had a malignant lesion ($P < 0·01$).

Gallstones were present in 40 of 159 benign lesions (25·2 per cent), but in seven of 13 malignant lesions ($P < 0·05$). Malignant lesions were found in seven of 47 PLG with cholecystlithiasis, but in only six of 125 (4·8 per cent) PLG without gallstones ($P < 0·05$)

Of the 182 patients with ultrasonographic and/or pathological diagnosis of PLG, 180 underwent cholecystectomy, which accounted for 12·1 per cent of the 1482 gallbladders removed surgically in this period. Simple cholecystectomy was performed in 154 of 159 cases with benign lesions; the other five patients underwent partial cholecystectomy In 13 patients with malignant lesions, radical cholecystectomy[5,6] was performed according to the stage of the gallbladder cancer, except in two cases with distant metastases. Symptoms were relieved following operation in all patients, with the exception of these two cases with advanced cancer One case was complicated by an incisional hernia after cholecystectomy

Discussion

The frequency of PLG reported in the literature varies from 0·004 to 13·8 per cent of resected gallbladders[2,7] and is

12·1 per cent in the present paper. PLG are found most often in the third, fourth and fifth decades of life, and they occur in both sexes The terminology or classification of PLG remained controversial until the report of Christensen and Ishak[1]. It is apparent from the present report that most PLG are benign lesions; malignant lesions accounted for only about 8 per cent The majority of benign lesions are pseudotumours, of which more than half are cholesterol polyps. Conversely, adenoma, a true neoplasm, accounts for only about 8 per cent of PLG in this series, much lower than that reported by Christensen and Ishak[1]. This difference is perhaps due to the increased detection of cholesterol polyps by ultrasonography.

The preoperative diagnosis of PLG includes detection and differentiation of benign and malignant polyps. The symptoms of PLG are not specific. About one-sixth of cases with the lesions are asymptomatic, and are detected incidentally by ultrasonography. Approximately five-sixths of cases complain of symptoms similar to those of chronic cholecystitis and cholelithiasis. Therefore a preoperative diagnosis of PLG is mainly dependent on diagnostic imaging by ultrasonography, oral cholecystography, CT and ERCP. It has been reported that the general sensitivity of ultrasonography in detecting PLG ranges from 45·1 to 84·0 per cent[3,4,8]. It was 90·1 per cent in this series, reaching 99 2 per cent in the detection of PLG in patients without gallstones. The specificity of ultrasonography was 93·9 per cent Therefore the accuracy of ultrasonography in the investigation of PLG is superior to that of CT, oral cholecystography and ERCP In addition, ultrasonography can more accurately demonstrate the location, size and number of PLG and changes in the gallbladder wall. Ultrasonography is therefore the investigation of first choice for the diagnosis of PLG, particularly for the investigation of PLG without gallstones in the gallbladder. Although some factors such as the presence of gallstones and mucocele of the gallbladder may limit the use of ultrasonography with a few false negative and false positive interpretations, preoperative diagnosis of PLG in this unit now depends entirely on repeated ultrasonographic examination.

Although PLG can be precisely demonstrated by ultrasonography, and changes in PLG are readily detectable with repeated ultrasonographic examination, there is still no effective and reliable test to differentiate malignant from benign lesions before operation. The results from this study clearly confirm that the size and number of PLG, the age of patients and the presence of gallstones correlate closely with the nature of PLG, and these characteristics are helpful in differentiating malignant from benign lesions before operation Therefore a malignant condition should be carefully considered when PLG are >1·0 cm in diameter, when PLG are single in number, when patients with PLG are over the age of 50 years, or when PLG are associated with cholecystlithiasis.

The treatment of choice for PLG depends mainly on the clinical symptoms and histological type. One adenoma was associated with atypical hyperplasia, and four adenomas had undergone malignant transformation, which supports the concept that adenoma is a precancerous lesion[9], and should be resected prophylactically. However, none of the pseudotumours in the gallbladder, including cholesterol polyps, inflammatory polyps and adenomatous hyperplasia, had undergone malignant transformation Therefore, theoretically, those lesions do not require operation. In view of the fact that it is still difficult to differentiate malignant from benign lesions before operation, it is concluded from the present study that the indications for operation for PLG should be PLG exceeding 1·0 cm in diameter, PLG being single in number, PLG associated with gallstones, patients with PLG over 50 years of age, or the presence of apparent clinical symptoms of PLG. However, asymptomatic patients with PLG <1·0 cm in diameter can be followed up and observed at intervals of 3–6 months with ultrasonography because the tumour may grow rapidly[10]. If an increase in size is demonstrated on follow-up, cholecystectomy should be performed immediately.

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Parietal seeding of carcinoma of the gallbladder after laparoscopic cholecystectomy

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The incidence of carcinoma of the gallbladder in autopsy series ranges from 0·18 to 0·81 per cent[1,2]. In patients operated on for biliary tract diseases, carcinoma of the gallbladder is found in 1–2 per cent of cases[3,4]. A preoperative diagnosis may be made in as few as 10 per cent of cases[1]. As laparoscopic cholecystectomy is increasingly used[5,6], it is probable that carcinoma of the gallbladder will be removed by this technique.

We report here a case of parietal seeding of a carcinoma of the gallbladder after laparoscopic cholecystectomy.

Case report

A 58-year-old woman was admitted in June 1990 with a 5-day history of right upper quadrant pain and fever. She was known to have gallstones, diagnosed 10 years earlier, with repeated episodes of pain during the last year. Physical examination showed tenderness of the right upper quadrant with no palpable mass. The temperature was elevated at 38·5°C. Investigations showed a white blood cell count of 7·04 × 10^9/l with 85 per cent neutrophilia. Ultrasonography showed a distended gallbladder with a thickened but regular wall, multiple stones less than 10 mm in diameter, and no dilatation of the biliary tree. Laparoscopic cholecystectomy was performed using three trocars: the videolaparoscope was introduced through a 10-mm laparoscopic trocar placed in a periumbilical incision, another 10-mm trocar was inserted in the left upper quadrant midway between the xiphoid process and the umbilicus, the third trocar was placed in the right iliac fossa for retraction of the gallbladder. The gallbladder was inflamed with necrotic areas and contained 100 ml of pus. There was no other intra-abdominal lesion. Although the dissection was difficult owing to inflammation, the gallbladder was removed intact and there was no spillage of bile. A peritoneal lavage was performed at the end of the operation. The duration of operation was 150 min. There was no macroscopic evidence of tumour on the gallbladder. Histological examination revealed a poorly differentiated carcinoma of the gallbladder infiltrating the whole thickness of the gallbladder wall, associated with perineural and vascular invasion (stage 3)[7]. The patient left hospital on the fifth day after operation. Postoperative computed tomography showed no liver metastases. Postoperative radiotherapy of 45 Gy was given to the tumour site in 25 sessions over 6 weeks. The patient was seen in October 1990 with a complaint of periumbilical pain. Physical examination revealed a 3-cm umbilical mass and a 1·5-cm nodule on the left trocar incision. The two nodules were removed, exploration of the abdomen disclosed several nodules of omental carcinomatosis and multiple liver metastases. Histological examination of the parietal nodules confirmed that they were metastases from the carcinoma of the gallbladder. The patient died from progression of the disease in March 1991.

Discussion

In this case, laparoscopic cholecystectomy seemed justified because acute cholecystitis is not a contraindication for this procedure[8]. Preoperative diagnosis of carcinoma of the gallbladder is rarely made[2,9,10]. The lack of diagnostic images on ultrasonography is frequent in carcinoma of the gallbladder, with 60–90 per cent of the cases presenting as acute cholecystitis[11,12]. Peroperative diagnosis of carcinoma is also difficult and was made in only 40 per cent of the patients in one series[2]. In the case reported, diagnosis was made after histological examination of the gallbladder. The parietal seeding on the periumbilical incision could be due to the passage of the laparoscope or, more likely, to the extraction of the gallbladder through this incision. The parietal seeding at the site of the left trocar insertion could be explained by the frequent changes of instruments passed through this trocar or by seeding along the drain. Parietal seeding of lung, thyroid, prostate and ovarian cancers has been reported after fine needle or laparoscopic biopsies[13–17], but the frequency of this complication is low (0·08 per cent)[16]. To our knowledge, this complication has not yet been described after laparoscopic cholecystectomy. Its prevention seems difficult. Due to the low incidence of carcinoma of the gallbladder and its dismal prognosis whatever the treatment, it seems unreasonable to consider an inflammatory mass of the gallbladder as a contraindication to laparoscopic cholecystectomy. When the diagnosis of carcinoma of the gallbladder is made after operation, we suggest that either surgical resection or postoperative irradiation of the trocar sites should be included in any supplementary treatment.

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Case report

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Bile duct injury following laparoscopic cholecystectomy

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Laparoscopic cholecystectomy has been introduced without the caution normally accorded to a new technique and without a controlled study comparing it to the conventional operation. The overall safety of the procedure appears to be similar to that of conventional cholecystectomy but bile duct injury may be more common[1,2]. Two cases are reported to emphasize the importance of this complication and to stress the need for careful surveillance of the safety of the procedure.

Case reports

Patient 1

A 59-year-old woman was referred with a biliary stricture which developed 3 months after laparoscopic cholecystectomy. At the original operation, the cystic duct was noted to be short and it was thought to insert directly into the right hepatic duct. It was dissected and titanium clips were applied. After operation the patient developed a biliary fistula which closed spontaneously after 2 weeks. Three months later she presented with right hypochondrial pain and obstructive jaundice. A percutaneous transhepatic cholangiogram showed obstruction of the common hepatic duct and thereafter the patient became deeply jaundiced and febrile.

Liver function tests showed a bilirubin level of 234 μmol/l, alkaline phosphatase of 1320 units/l and aspartate transaminase of 31 units/l. A second percutaneous transhepatic cholangiogram showed a tight stricture immediately below the origin of the common hepatic duct (*Figure 1*) and a biliary leak from the previous cholangiography puncture site. Coeliac axis angiography excluded any hepatic vascular injury. At laparotomy, the peritoneal cavity contained 2 litres of bile. There were extensive adhesions, especially to the gallbladder bed. The stricture was identified just below the level of the biliary convergence and appeared to be related to a titanium clip. This Bismuth type III stricture was excised and a hepaticojejunostomy Roux-en-Y performed. The patient recovered uneventfully and was discharged 1 week later. A postoperative ^{99m}Tc-EHIDA (iminodiacetic acid derivative) scan showed good biliary excretion with no anastomotic narrowing or leakage.

Patient 2

A 33-year-old woman was referred for assessment and management of a persistent subphrenic bile collection 3 weeks after laparoscopic cholecystectomy. There had been difficulty in identifying the ductal anatomy and two ductal structures were divided which seemed to communicate with the gallbladder. The patient developed persistent right upper quadrant pain and ultrasonography showed a subhepatic bile collection which was drained and a biliary tree of normal calibre. Endoscopic retrograde cholangiopancreatography demonstrated a normal common bile duct and left hepatic ductal system. There was extravasation of contrast close to the clipped cystic duct which filled a large cavity and eventually opacified the right ductal system. The patient was referred with established sepsis.

Results of liver function tests were normal apart from a raised alkaline phosphatase level (489 units/l). Coeliac axis angiography excluded any vascular injury. At laparotomy the proximal injured end of the right hepatic duct was draining freely into a large subhepatic cavity. Intraoperative cholangiography (*Figure 2*) confirmed an injured right hepatic with a normal left ductal system. A right hepaticojejunostomy Roux-en-Y was performed. The postoperative course was complicated by a wound infection and psychotic depression.

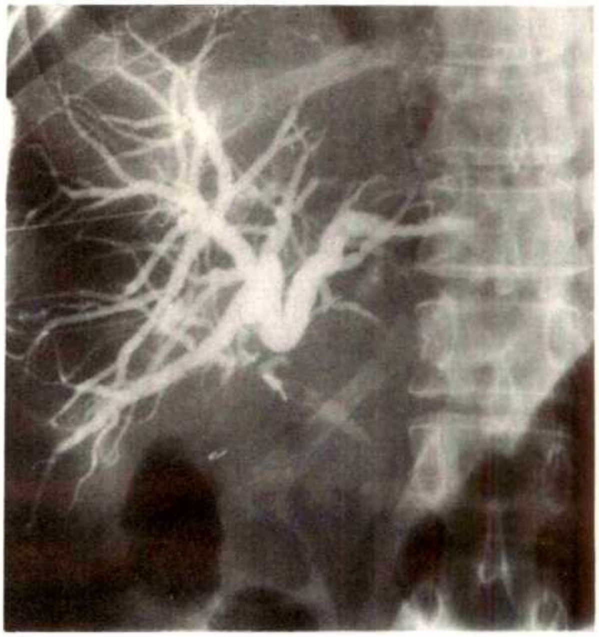

Figure 1 *Percutaneous transhepatic cholangiogram showing a dilated intrahepatic biliary system with obstruction at the liver hilum just below the biliary convergence. Note the presence of titanium clips just below that level*

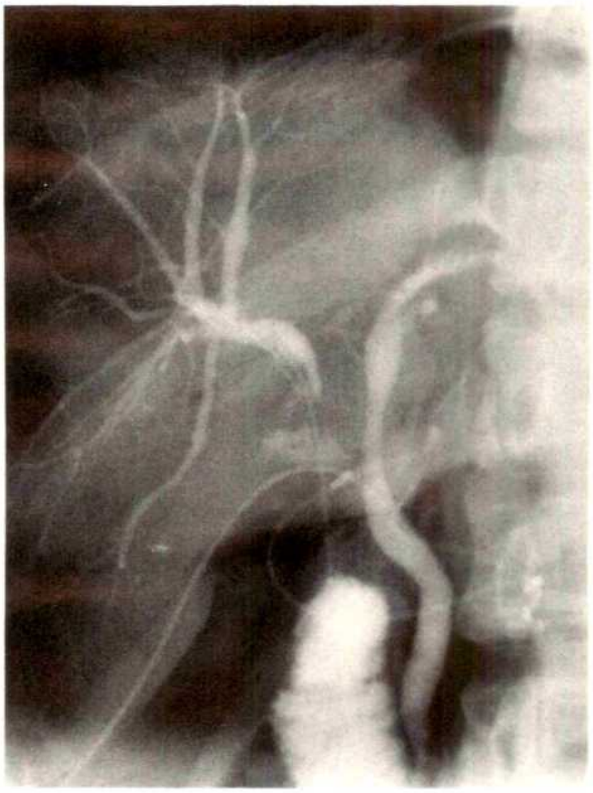

Figure 2 *Intraoperative cholangiogram showing the right and left hepatic ductal systems. The right hepatic duct was cannulated through its open end and the left ductal system was shown by injecting contrast via the cystic duct after removal of its titanium clip*

Discussion

There is minimal morbidity following conventional cholecystectomy, and bile duct injuries occur in 0·1–0·4 per cent of cases[3,4]. The incidence of bile duct injury following laparoscopic cholecystectomy may be higher. Despite the advantages of the technique, its use may not be justified if it proves to be less safe than the conventional operation.

The cases reported illustrate two important points. Not all bile duct injuries are apparent at the time of cholecystectomy or in the immediate postoperative period. The first patient presented with jaundice 3 months after the operation. The biliary fistula was assumed to be due to drainage from an accessory duct or the cystic duct and resolved spontaneously. In fact, a titanium clip was partly occluding the common hepatic duct which with stricturing due to the trauma led to complete obstruction. In both patients there was difficulty in identifying the bile duct anatomy which the surgeon thought to be anomalous. In the first patient, the duct may have been caught while clipping another structure, but in the second the right hepatic duct appears to have been mistaken for the cystic duct which was identified later in the operation. Peroperative cholangiography has been abandoned by most surgeons who perform laparoscopic cholecystectomy because of technical difficulty and the extra time taken. Cholangiography is useful for determining the ductal anatomy and may have prevented injury. If cholangiography is not performed then conversion to open operation should occur when there is uncertainty in identification of ductal anatomy. Angiography was performed in both patients before re-exploration because associated vascular injuries can cause bile duct ischaemia, affecting anastomotic healing and future stricturing. In a series of 78 patients with postcholecystectomy bile duct strictures, 19 of 25 patients undergoing angiography because of a history of operative vascular injury showed evidence of arterial or portal injury[5]. In these patients, the anastomosis is best performed at the liver hilum even if there is normal duct below.

It is probably no longer feasible to perform a controlled trial comparing new and old techniques of cholecystectomy[6]. The morbidity of the procedure, particularly from bile duct injury, needs to be accurately audited on a national scale to assess the incidence, reasons for injury and how the complication can be avoided.

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Laparoscopic cholangiography: an effective and inexpensive technique

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The practice of intraoperative cholangiography as an adjunct to laparoscopic cholecystectomy varies[1–4]. Several techniques have been described but all require special instrumentation or purpose-designed and expensive cannulae. A simple and effective technique for the procedure is described which requires no special equipment or instrumentation beyond that routinely available in the operating theatre for laparoscopic surgery.

Surgical technique

During laparoscopic cholecystectomy the normal arrangement of instruments is for the telescope to occupy the subumbilical cannula, the fundus of the gallbladder to be steered towards the diaphragm by a grasping forceps in the anterior axillary cannula and for the remaining midline epigastric and mid-clavicular cannulae to be used for the surgeon's instruments. Practice in this unit is to use an atraumatic grasping forceps on Hartmann's pouch to prevent tearing of the gallbladder wall.

Operative cholangiography is performed by introducing a Cava-Fix cannula (Braun, Melsungen, Germany) through the abdominal wall between the mid-clavicular and anterior axillary cannulae (under direct vision). The cost of the cannula at the time of writing is around £200 for 50 (£4·22 each). The cystic duct is occluded at the gallbladder end with a Ligaclip (Ethicon, Edinburgh, UK), introduced via the midline epigastric cannula. The cystic duct is opened distal to the gallbladder using microscissors. A fine forceps is then introduced through the midline epigastric cannula which is used to pick up the cholangiogram cannula. The fundus-holding forceps (anterior axillary cannula) is transferred to hold the gallbladder just above Hartmann's pouch and tension is maintained (*Figure 1*). The fine forceps (midline epigastric cannula) is then used to steer the cholangiogram cannula into the cystic duct, whereupon the atraumatic forceps from Hartmann's pouch (mid-clavicular cannula) is transferred to hold the cholangiogram cannula in place, and to seal the orifice of the cystic duct (*Figure 2*).

Two points of technique facilitate difficult cannulation. First, if there is too small an opening in the cystic duct this may be dealt with by introducing the tip of the microscissors into the orifice and then opening them, thus stretching the hole. This avoids the risk of dividing a small duct by cutting it further. Second, the cannula should be presented to the duct at right angles and not obliquely; once the cannula tip is engaged in the orifice the angle can be changed to allow deep penetration of the cystic duct. Some surgeons bevel the cannula tip with scissors to make introduction easier although this is not routinely done in this unit because the cannula is more likely to get caught up in the spiral valve or to perforate the posterior wall of the cystic duct.

Once the cannula has been placed the stilette is removed while the cannula is kept in vision; this often requires slight relaxation of the grasp of the forceps. Bile usually fills the cannula as the stilette is withdrawn but slight aspiration with a syringe will fully clear the duct of air bubbles. Saline is then flushed through the cannula to ensure that there is no leakage (again relaxing the grasp of the forceps slightly) and the syringe containing contrast (Omnipaque; iodine 300 mg ml^{-1}, Nycomed, Birmingham, UK) is attached to the cannula ready for cholangiography. Instruments are withdrawn under direct vision with the exception of the forceps holding the cannula in place, and the laparoscope is then withdrawn.

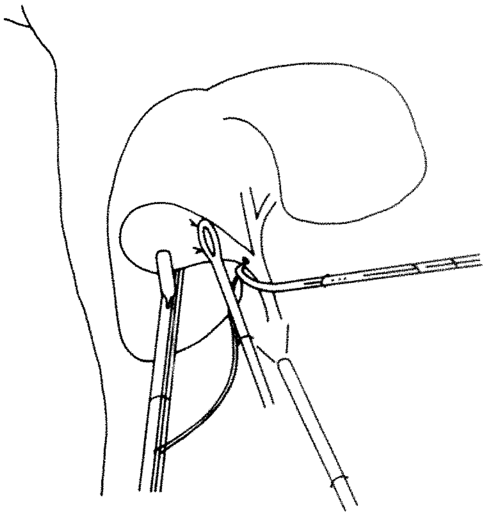

Figure 1 *The cannula has been introduced through the abdominal wall between the anterior axillary and mid-clavicular cannulae. The fine forceps (midline epigastric cannula) is holding the cannula over the opened cystic duct. The fundus-holding forceps (anterior axillary cannula) is being transferred to hold Hartmann's pouch so that tension is maintained as the mid-clavicular forceps is transferred to the cystic duct*

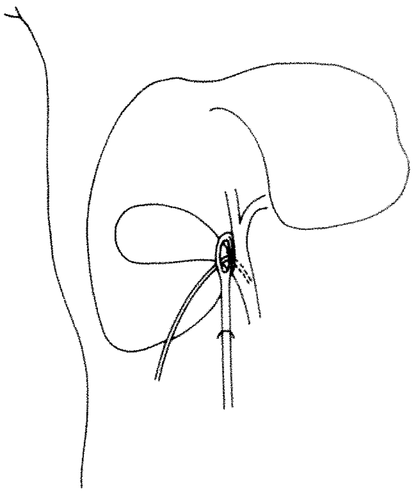

Figure 2 *The final position. The cannula has been introduced into the cystic duct and the mid-clavicular forceps is holding it in position. The other instruments have been removed*

Radiographic technique may be adapted according to available resources. Conventional films may be exposed, a method used in this unit with success. Alternatively, C-arm screening using the image intensifier with hard-copy capability has several advantages. First, the beam can be easily centred in the correct site. Second, the volume of contrast to give the best image can be precisely titrated (this will vary according to duct size). Third, any overlap between radio-opaque instruments and the bile duct can be dealt with. Fourth, and perhaps most importantly, any distortion of the duct by the cannula or by the forceps can be corrected, otherwise radiographs suggesting incorrect anatomy or common bile duct or hepatic duct occlusion may be obtained (*Figures 3* and *4*). If C-arm screening is not available, two further technical variations may facilitate successful cholangiography. First, the cannula may be secured with a 9-mm Ligaclip to reduce distortion of the duct. This method is not routinely used because the forceps gives better control over the cholangiogram cannula. Second, the midline epigastric cannula may either be removed over a radiolucent

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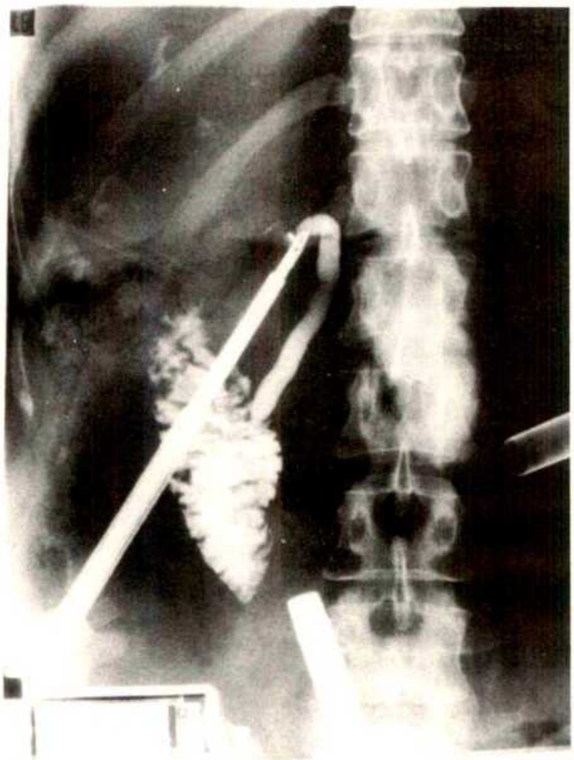

Figure 3 *Cholangiogram showing apparent occlusion of the common hepatic duct due to tension on the forceps*

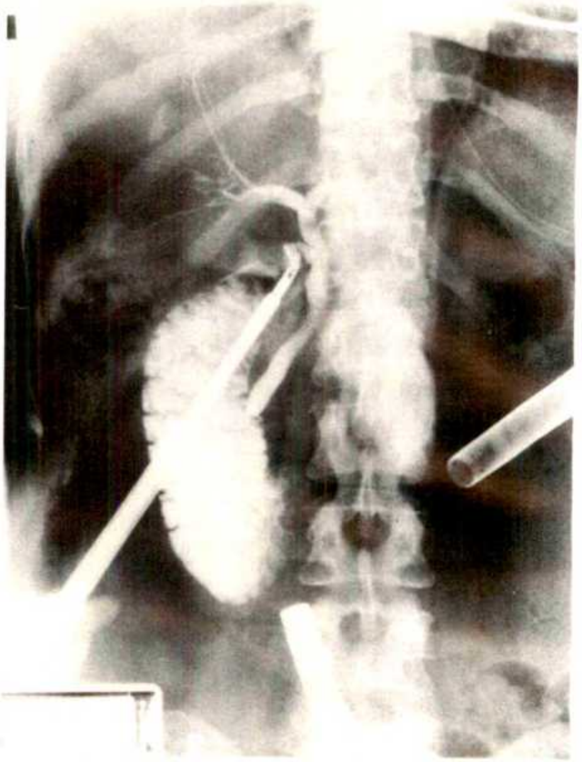

Figure 4 *Repeat cholangiogram with forceps adjusted to show normal duct*

rod or replaced by a radiolucent disposable cannula to prevent superimposition of the steel cannula.

Discussion

This unit has pursued a prospective policy of operative cholangiography at laparoscopic cholecystectomy for gallstones. Successful cannulation of the cystic duct has been achieved in 32 of 35 attempts using the technique described, the ease and speed of cannulation having undoubtedly improved with practice. Failures have been due to an obliterated cystic duct (two cases), and cannulation of Hartmann's pouch (one case) where cholangiography allowed confirmation of anatomy during a difficult dissection. The technique described is commended for its simplicity and effectiveness.

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Extracorporeal shockwave lithotripsy and litholytic therapy in cholelithiasis

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Extracorporeal shockwave lithotripsy (ESWL) and litholytic therapy were used in 100 patients over a period of 16 months. ESWL was carried out with a Lithostar Plus and chenodeoxycholic acid was used as the lytic agent, given until 3 months after complete disappearance of stones. Within a period of 8–12 months, stones disappeared completely in 82 per cent of the patients who had a single stone ≤20 mm in diameter and in 50 per cent of those with a single stone >20 mm in size or with multiple stones. Complications requiring surgery developed in five patients: three had acute cholecystitis and two developed acute pancreatitis. Of the patients in whom complete stone clearance was achieved, two of 11 followed up developed recurrence of stones 4 months after cessation of lytic therapy.

Cholelithiasis is an important health problem. Clinical, epidemiological and necropsy studies have revealed a morbidity rate of 15–20 per cent associated with stones of the biliary tract in adults[1]. The first cholecystectomy was performed in 1882[2]; it is now the most widely practised and safest mode of treatment[3–8]. The introduction of chenodeoxycholic acid and ursodeoxycholic acid allowed non-operative therapy to become a popular method for treating cholelithiasis[9]. Percutaneous methyl *tert*-butyl ether and mono-octanoin have also been used to dissolve stones[9,10]. Successful treatment of gallstones with extracorporeal shockwave lithotripsy (ESWL) has been reported[5,11–13]. This paper presents the results of treating 100 patients with ESWL and lytic therapy.

Patients and methods

A total of 276 patients were referred between July 1989 and October 1990 with cholelithiasis. Of these, 100 patients were suitable for ESWL and lytic therapy according to the criteria in *Table 1*. There were 73 women and 27 men (mean age 50·6 (range 9–78) years). Of the patients 73 had a single stone, 11 had two, eight had three and eight had four to ten stones. Of the patients with a solitary stone, in 60 this was ≤20 mm in diameter.

Blood count, bleeding, clotting and prothrombin time, routine urine analysis, chest radiography and oral cholecystography were repeated on the third and seventh day of ESWL. Oral chenodeoxycholic acid (10 mg kg^{-1} day^{-1} single dose after dinner) was started 12 days before ESWL and continued for 3 months after the disappearance of all stones. ESWL used a Lithostar Plus (Siemens, Munich, Germany). The procedure was carried out with the patients in the left lateral decubitus position. Stones were fragmented to 4 mm, the procedure being repeated once or twice at 2-week intervals until this fragment size was achieved. No patient received more than three ESWL treatments. When the patients complained of pain, intravenous pethidine (30–50 mg) was given. A group of 54 patients received a single treatment with ESWL, 30 patients two treatments and 16 patients three treatments. In cases where a single session was successful, a mean of 2400 (range 1235–4000) shockwaves was administered. In cases requiring more than one treatment, a mean of 3900 (range 3200–4500) shockwaves was administered per treatment. In cases where the stones could not be fragmented by three ESWL sessions, the procedure was judged unsuccessful and treatment was discontinued. The first 30 patients were hospitalized for 1–3 days after treatment; thereafter the procedure was performed on an outpatient basis. Statistical analysis was carried out using the χ^2 test.

Results

Adequate fragmentation occurred in 96 patients; in four cases fragmentation did not occur. (Patients were followed for 2–18 months.) Fragmentation was achieved in 71 of 73 patients (97 per cent) with a single stone. The stones disappeared completely in 33 patients (45 per cent) but could not be fragmented in two (3 per cent) even after three ESWL sessions. Fragmentation was accomplished in nine of 11 patients with two stones and in four of these the stones disappeared completely. In patients with three stones all fragmented and in two cases disappeared completely. In the group of eight patients with four to ten stones fragmentation was accomplished in all and stones disappeared completely in three. These results are summarized in *Table 2*. Dissolution of stones was achieved in a shorter period of time in those with single stones ≤20 mm in diameter (*Table 3*).

Complications are shown in *Table 4*. These were observed 7–32 days after ESWL. The two patients with acute pancreatitis underwent cholecystectomy and choledochal drainage. Cholecystectomy was performed in the three patients who developed acute cholecystitis. There were no deaths. Eleven patients with complete disappearance of all fragments have been followed for up to 4 months after cessation of chenodeoxycholic acid

Table 1 *Criteria for selection of patients for lithotripsy*

1. A history of biliary pain
2. Presence of not more than three stones*
3. Presence of radiolucent stones
4. Presence of stones <30 mm in diameter
5. Presence of a functioning gallbladder
6. Proper visualization of the gallbladder and the stone by ultrasonography
7. Absence of pulmonary tissue, cyst, or aneurysm between the gallbladder and the shockwave path
8. Absence of cholecystitis, pancreatitis, stone in common bile duct, biliary obstruction, chronic hepatic disease, haemorrhagic diathesis, pregnancy or pacemaker

*Criterion not observed in eight patients

Table 2 *Fragmentation and disappearance of gallstones*

No. of gallstones	No. of patients	Fragmentation	Disappearance
1	73	71	33
2	11	9	4
3	8	8	2
4–10	8	8	3

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Table 3 *Time to disappearance of gallstones*

	Patients with single stones ≤ 20 mm in size		All other patients combined	
Time (months)	*n*	Stone disappearance	*n*	Stone disappearance
2	60	23	40	0
4	48	29*	37	9
8	38	28*	27	11
12	28	23*	6	3

$^*P < 0{\cdot}05$ (single stones ≤ 20 mm in size *versus* all other patients combined, χ^2 test)

Table 4 *Complications*

	n
Cutaneous petechiae or ecchymosis	14
Transient haematuria	6
Biliary colic	54
Diarrhoea	5
Acute pancreatitis	2
Acute cholecystitis	3

therapy. At the 4-month visit, two of these 11 patients were noted to have recurrence of gallstones.

Discussion

Of all patients with gallstones 10–25 per cent meet standard published criteria for ESWL treatment[12,13]. In the patients in this series with up to three stones, 33 per cent met the published criteria for ESWL. Some authors have performed ESWL on patients with as many as ten stones provided the other criteria were met[14,15]. Eight such patients were included in this series.

In the present study, the size of the stone seemed to be the principal factor in the successful treatment of cholelithiasis with ESWL and chenodeoxycholic acid. An evaluation of the complete disappearance of stones revealed that single stones ≤ 20 mm in size disappeared within 1 year at a rate of 82 per cent, this rate being 50 per cent when results from all other patients were combined. This is a statistically significant difference ($P < 0{\cdot}05$). There were no significant differences between the time to dissolution in the other groups with larger or multiple stones. Lithotripsy proved especially successful with single stones ≤ 20 mm in size. These results are confirmed by other reports[11–14].

In the present study, 46 per cent of patients received multiple ESWL treatments, a similar proportion to that in the series of Ponchon *et al.*[14] (46 per cent), Ell *et al.*[16] (48 per cent) and Hood *et al.*[17] (66 per cent) but higher than in the study by Sackmann *et al.*[12] (5 per cent).

Complication rates were similar to those from other reports although biliary colic was frequent, as described by Burnett *et al.*[18]. Acute pancreatitis following ESWL was reported at a rate of 0–3 per cent[12,14,17,19–21] (2 per cent in this series) and cholecystectomy at a rate of 4–6 per cent[14,20] (5 per cent in this series).

Recurrence of gallstones may be observed after ESWL. After oral bile acid treatment recurrence may be as high as 61 per cent at the end of the 11th year[22]. Some have reported this rate to be 9·3 per cent at 1 year and 11·4 per cent in 3 years[23,24]. In this series the recurrence rate was 18 per cent in the first 4 months and may be due to patients not taking chenodeoxycholic acid therapy regularly or to technical errors during evaluation of residual fragments at the end of lithotripsy.

None of the methods of treatment retaining the gallbladder, such as ESWL, alters the lithogenic character of the bile. The percentage of patients who will remain stone-free is not clear. ESWL has moderate efficacy especially in patients with a single stone ≤ 20 mm in size. Non-operative therapy may not replace surgery for gallstone disease because of cost and the high recurrence rate. ESWL is not a definitive treatment for gallstones but may offer a temporary solution.

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Short note

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Percutaneous gallbladder drainage for acute acalculous cholecystitis during total parenteral nutrition

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Total parenteral nutrition (TPN) has been shown to cause progressive abnormalities in gallbladder motor function which may lead to biliary sludge formation and ultimately to gallstones. Acute acalculous cholecystitis is a recognized complication of TPN[1,2], and 40–100 per cent of such patients with acute acalculous cholecystitis will have advanced disease with gangrene, empyema or perforation of the gallbladder[3,4].

Early cholecystectomy has been suggested for patients with TPN-induced acute cholecystitis[5]. Urgent surgery, however, has a high risk of complications, especially in a patient receiving TPN who usually has other complicated surgical problems[2,6]. We report the results of ultrasonographically guided percutaneous drainage without laparotomy as an alternative method to treat patients with TPN-induced acute cholecystitis.

Patients and methods

Six patients who received TPN in the management of various postoperative complications developed acute cholecystitis and underwent ultrasonographically guided percutaneous gallbladder drainage during the past 5 years (*Table 1*). All developed fever, leucocytosis and right upper quadrant abdominal pain during treatment with TPN. Abdominal ultrasonography was performed. Acute cholecystitis with a distended, thick-walled gallbladder and bile sludge was found in all patients. The gallbladder was also always in close contact with the abdominal wall. Ultrasonographically guided percutaneous drainage by direct puncture of the gallbladder was performed in each patient in preference to a second, emergency operation.

Under local anaesthesia with lignocaine, an 18 Fr drainage catheter (Cliny Medical, Yokohama, Japan) was inserted directly into the gallbladder with sonographic guidance. The infected bile was aspirated and sent for culture. The gallbladder became smaller, and under sonographic control irrigation with normal saline was performed carefully through the catheter until the sludge had been washed out. Ultrasonography was used to demonstrate that the gallbladder had collapsed (*Figure 1*). Culture of aspirated bile grew pathogenic organisms in every case; *Escherichia coli* was isolated from six patients and *Enterococcus* was isolated from one.

Table 1 *Sex, age, operative procedure and day of onset of symptoms after start of TPN of six patients with acute cholecystitis*

Patient no.	Sex	Age (years)	Previous operation	Onset (days of TPN)
1	M	55	Subtotal gastrectomy	10
2	F	25	Colon interposition	14
3	M	67	Total gastrectomy	20
4	M	50	Subtotal gastrectomy	16
5	M	54	Vagotomy and pyloroplasty	18
6	M	63	Devascularization for bleeding varices	12

TPN, total parenteral nutrition

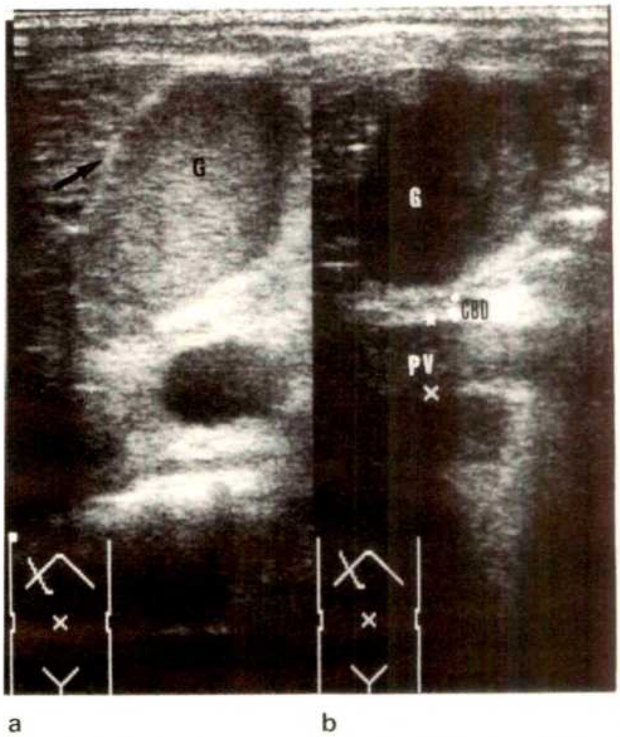

Figure 1 **a** *Acute cholecystitis due to bile sludge; note thickened gallbladder wall (arrow), about 3 mm in thickness.* **b** *Following ultrasonographically guided percutaneous drainage with irrigation and aspiration of sludge, the gallbladder (G) became smaller. CBD, common bile duct; PV, portal vein*

Patients reported immediate symptomatic improvement after the procedure. The catheter was retained with secure fixation for 1 or 2 days, and was then removed. The patients' symptoms subsided and recovery was uncomplicated in every case. No patient had recurrence of cholecystitis after treatment.

Discussion

The diagnosis and treatment of gallbladder disease in a patient receiving TPN needs caution. Most patients receiving long-term TPN in the surgical ward have had previous operations and have suffered postoperative complications. The laboratory evaluation of gallbladder disease may be made difficult by various conditions which disturb liver function. Abdominal ultrasonography has been shown to be a reliable technique for the diagnosis of both acalculous and calculous gallbladder disease in patients receiving TPN[4,6]. Because they usually have complex medical problems and have had a recent laparotomy, cholecystectomy for such patients carries a high risk. They usually have some degree of TPN-induced liver impairment and coagulation abnormalities[7,8]. Operative morbidity and mortality rates in these patients may be as high as 54 and 11 per cent respectively[2]. An alternative procedure to cholecystectomy may be desirable, especially for patients who have a high risk for general anaesthesia or operation.

Ultrasonographically guided drainage of the distended gallbladder could avoid an emergency operation. Either a transhepatic approach or direct transcutaneous puncture is appropriate. The former carries no risk of bile leakage, but bleeding from the liver surface is a risk for patients who have an acute inflammatory condition. The direct approach is easier and the risk of bile leakage is low because of surrounding

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adhesions resulting from acute inflammation and prior upper abdominal surgery. Leakage can also be reduced by rapid decompression of the gallbladder contents. The catheter is left in place after the aspiration and irrigation to reduce the risk of leakage from the puncture hole in the gallbladder wall.

If the procedure is performed during the early stages of acute cholecystitis, the risk of gangrenous changes of the gallbladder is low. An emergency operation should be carried out if the patient's symptoms do not improve after the drainage procedure or if they recur after drainage or removal of the catheter. The reasons for emergency surgery are the rare possibility of gangrenous changes of the gallbladder and intra-abdominal bleeding or bile spillage after the drainage procedure. However, in the patients discussed the diagnosis and drainage of the distended gallbladder was achieved at an early stage when the risk of gangrenous changes was low, and there were no complications of the drainage procedure.

Percutaneous ultrasonographically guided drainage is not recommended as a substitute for cholecystectomy in all cases of cholecystitis induced by TPN. It can be considered when the patient is not suitable for an emergency operation or if the patient is unwilling to consent to reoperation soon after a previous operation. If the timing after onset of symptoms is early, percutaneous drainage is safe and effective for the acutely ill patient.

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Combined whole pancreas and liver retrieval: a new technique for arterial reconstruction of the pancreas graft

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Over the past 10 years, the results of pancreas transplantation have undergone significant improvement[1]. Whole pancreaticoduodenal transplantation, however, requires retrieval of the entire pancreas with its blood supply dependent on the coeliac axis, superior mesenteric artery (SMA) and portal vein. Therefore it was originally thought that whole pancreas retrieval was possible only if the liver was not used for transplantation. With the current increase in numbers of liver and pancreas transplants, many groups have found it necessary to develop techniques for the combined retrieval of the intact pancreas and duodenum, as well as the liver[2,3]. A total of 35 consecutive multiorgan retrievals including liver, pancreas, heart and kidneys have been carried out in this hospital. A simpler method of arterial reconstruction for the pancreatic graft has recently been developed and is reported here.

Surgical technique

In this hospital organ retrieval is initiated by the cardiac surgeon who first mobilizes the great vessels. The first step in combined liver–pancreas retrieval is to obtain control of the distal aorta and distal inferior vena cava. The anatomy of the hepatic blood supply is assessed at this stage. The presence of an aberrant right or left hepatic artery is not a contraindication to combined liver–pancreas retrieval. In this series one patient had an aberrant right hepatic artery and three patients had an aberrant left hepatic artery. With traction on the spleen, the body and tail of the pancreas are freed from their posterior attachments as far as the mesenteric vessels. The head of the pancreas and duodenum are mobilized by a standard Kocher manoeuvre. The common bile duct is ligated as close to the pancreas as possible. The inferior mesenteric artery and vein are identified and dissected free. The proximal branches of the jejunal arteries are ligated and divided. The portal vein is dissected free and the gastroduodenal artery is then ligated and divided. The proximal duodenum is closed with a linear stapler (GIA; Auto Suture, Norwalk, Connecticut, USA) and divided. The suprahepatic aorta is clamped and the liver and pancreas are flushed simultaneously with University of Wisconsin solution (UWS) through the aorta (2000–3000 ml) and the superior mesenteric vein (SMV) (500–1000 ml). The portal vein is divided 2 cm proximal to the pancreatic margin.

The common hepatic artery is mobilized to its origin from the coeliac axis, and the splenic artery is divided close to its origin. The splenic artery is marked with a 5/0 Prolene suture (Ethicon, Hamburg, Germany) to aid later identification. The hepatectomy is performed after removal of the heart. A Carrel patch of the donor aorta encompassing the origin of the coeliac axis is retained with the liver. The aorta is clamped above the SMA to allow *in situ* perfusion with cold UWS. The aorta, kidneys and ureters together with the pancreas, duodenum and spleen are removed. The aorta is opened longitudinally along its posterior wall and is divided below the origin of the SMA to separate the pancreas and kidneys. The pancreas is placed in iced Ringer's lactate and perfused with 300 ml UWS through the splenic artery and SMA. The stapled duodenal ends are oversewn with interrupted Lembert sutures. The distal SMV is suture ligated and the spleen is removed.

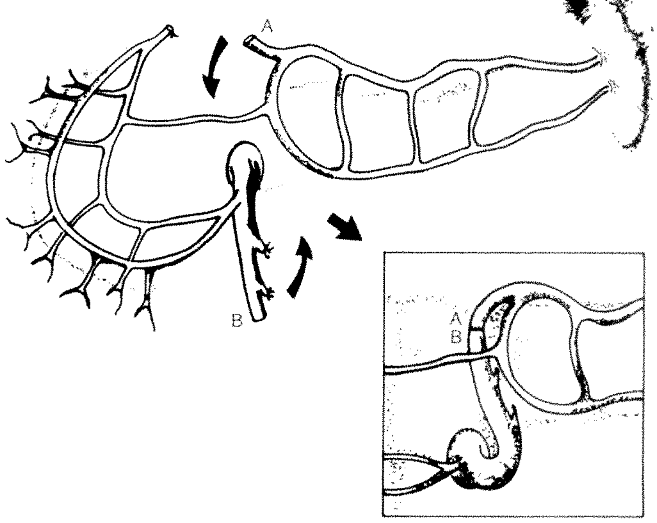

Figure 1 *Reconstruction of the arterial supply to the pancreas by end-to-end anastomosis between the proximal splenic artery and the distal end of the superior mesenteric artery*

The arterial supply of the pancreas is reconstructed with an end-to-end anastomosis between the proximal splenic artery and the distal end of the donor SMA (*Figure 1*). An end-to-side anastomosis is then made between the donor SMA and its aortic patch and the right iliac artery of the recipient. The portal vein is anastomosed to the right iliac vein and urinary diversion is performed by side-to-side duodenocystostomy. When the patient is undergoing simultaneous kidney and pancreas transplantation, the renal graft is inserted on the patient's left side.

Results

This technique has been used in ten patients. All simultaneous pancreas and kidney transplants functioned well initially with none of the patients requiring dialysis. All patients were insulin-independent immediately after surgery. One patient developed venous thrombosis in the graft, which had to be removed. This patient has subsequently undergone a successful second transplant. All patients are insulin-free 1–14 months after transplantation. Biochemical findings are shown in *Table 1*.

Table 1 *Laboratory findings in ten patients after pancreas transplantation with graft reconstruction using the technique of splenomesenteric anastomosis*

	Glucose (mmol l^{-1})	Serum creatinine (μmol l^{-1})	Serum amylase (units l^{-1})	Urinary amylase (units l^{-1})
Day 1	6·05(0·66)	5·72(1·76)	500(120)	40 000(7860)
Day 2	5·50(0·49)	2·20(0·79)	475(115)	110 000(29 000)
Day 3	5·39(0·33)	1·32(1·05)	375(88)	120 000(68 740)
Discharge	5·77(0·82)	1·23(0·88)	400(106)	130 000(54 000)

Values are mean(s.d.)

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Discussion

As increasing numbers of liver and pancreas transplants are being performed it has become necessary to develop a technique which allows simultaneous retrieval of both organs. In these circumstances the preservation of the arterial supply is a matter of controversy. Two techniques are available to vascularize the pancreatic graft. In the first, origins of the coeliac axis and the SMA are removed together with the pancreas on a common aortic patch, leaving the common hepatic artery to supply the liver graft. Some authors believe that the hepatic blood supply should be left undisturbed[4], and that the coeliac axis and its aortic patch should remain with the liver graft. In this case the splenic artery is transected after its origin from the hepatic artery, making it necessary to reconstruct the pancreatic arterial supply using one of the following techniques. The standard method uses the donor common iliac bifurcation for separate anastomoses to the splenic artery and SMA. There has been no arterial or venous thrombosis in 38 cases reported with this technique[5,6]. However this Y graft may not be suitable in the presence of atherosclerosis. Other described techniques involve end-to-side anastomosis of the splenic artery into the SMA with its aortic patch and end-to-side anastomosis between the coeliac artery and the proximal end of the SMA[7], but no results have been published. This simpler technique of arterial reconstruction with end-to-end anastomosis between the proximal end of the splenic artery and the distal end of the SMA is reported. This technique gives a much better size match and can be performed in almost all cases as long as care is taken to remove all excess connective tissue to allow anastomosis without tension. This is now our preferred technique for arterial reconstruction of pancreas grafts.

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Lymph node metastasis from early gastric cancer: endoscopic resection of tumour

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The clinicopathological features of 748 solitary early gastric cancers were examined with regard to lymph node metastasis. Among several factors, only depth of invasion and tumour size correlated significantly with node involvement. Tumours which satisfy the following criteria may not metastasize to lymph nodes: (1) confined to the mucosa; (2) less than 1·5 cm in diameter; (3) macroscopically elevated; (4) macroscopically depressed, without intramural ulcers or ulcer scars (endoscopically, no fold convergence); and (5) histologically differentiated. With a recently developed endoscopic technique small gastric tumours can safely be resected. The cut margin and depth of tumour invasion can be verified histologically in the specimen. If an endoscopically removed tumour satisfies the above criteria, further surgical intervention may be optional as the outcome of endoscopic resection is comparable to that of radical surgery in the absence of node involvement.

Early gastric cancers are, by definition, those whose invasion is limited to the mucosa (M-carcinoma) or the submucosa (SM-carcinoma), regardless of the presence or absence of lymph node metastasis[1]. This definition carries no chronological connotation and is more clinical in orientation than pathological, denoting a curable tumour endoscopically and surgically. The outcome of surgical treatment for early gastric cancer is excellent, confirming the notion that 'early' means 'curable'[2,3].

In Japan, gastrectomy with lymph node dissection is the standard treatment for early gastric cancer[4,5]. Widespread use of the fibreoptic endoscope has made it possible to detect extremely small cancers. The number of high-risk patients is increasing as the population ages. These situations demand modifications in surgical treatment for early gastric cancer.

A new endoscopic technique has recently been developed in Japan[6] which allows resection of polypoid and depressed lesions of the gastric mucosa (*Figure 1*). With this technique, however, there is the possibility of leaving positive lymph nodes around the stomach, thereby reducing the chance of a cure. Because most of the recurrences of early gastric cancer appear to be blood-borne metastases not amenable to surgical control[2,7,8], the outcome of endoscopic resection is, in the absence of node involvement, comparable to that of radical surgery. It is, therefore, essential to select patients without lymph node metastases for application of this technique.

In this study the clinicopathological features of early gastric cancers with reference to lymph node involvement were examined. The long-term goal was to determine the criteria justifying local surgery as an alternative to gastrectomy.

Patients and methods

From 1964 to 1990, 748 solitary early gastric cancers were resected in the First Department of Surgery, University of Tokyo, representing 36 per cent of all solitary resected gastric cancers. The proportion of early gastric cancers has increased over the years (*Figure 2*). Synchronous multiple early gastric cancers and those removed by local resection were excluded from the study.

Distal gastrectomy was performed in 677 patients (91 per cent), and total gastrectomy in the remainder except for five patients undergoing proximal gastrectomy. Dissected lymph nodes were classified by surgeons into numbered groups during or after operation. All macroscopic diagnoses of lymph node metastases were recorded. Resected stomachs were opened and fixed on a flat board in formalin, and the malignant lesions were examined with step sections. Depth of invasion, histological type and microscopic invasion into submucosal blood and lymphatic capillaries were recorded according to established methods. Each node was bisected and examined for evidence of metastasis.

The tumours were classified macroscopically using the system of the Japanese Gastroenterological Endoscopy Society (*Figure 3*). The size of the fixed specimen was considered to be the size of the tumour. For this study, the tumours were reclassified histologically as differentiated or undifferentiated adenocarcinoma. Differentiated adenocarcinomas were those with gland formation, papillotubular and tubular adenocarcinomas being included in this type. Undifferentiated adenocarcinomas lacked gland formation; poorly differentiated and signet ring cell carcinomas were included in this type. When both components were found in a tumour, the predominant type was recorded.

The Mann–Whitney U test and the χ^2 test were used for statistical analysis.

Results

Clinicopathological findings are summarized in *Table 1*.

Lymph node metastasis was confirmed pathologically in 77 of 748 cases (10·3 per cent). Intraoperative macroscopic diagnosis was correct in only 9 (12 per cent) of the 77.

Possible correlations between node involvement and several clinicopathological factors were examined. The following results were obtained.

Age and sex

Figure 4 depicts the age and sex distribution. All age and sex groups had similar incidences of node involvement.

Depth of invasion

Positive nodes were found in 14 (3·3 per cent) of 426 M-carcinomas and 63 (19·6 per cent) of 322 SM-carcinomas ($P < 0{\cdot}0001$). The pathological features of the 14 patients with M-carcinomas with positive nodes are listed in *Table 2*.

Tumour size

The mean size of the node-positive carcinomas was significantly greater than that of those which were node-negative. This was true at each depth of invasion (*Table 3*). Of 239 tumours whose

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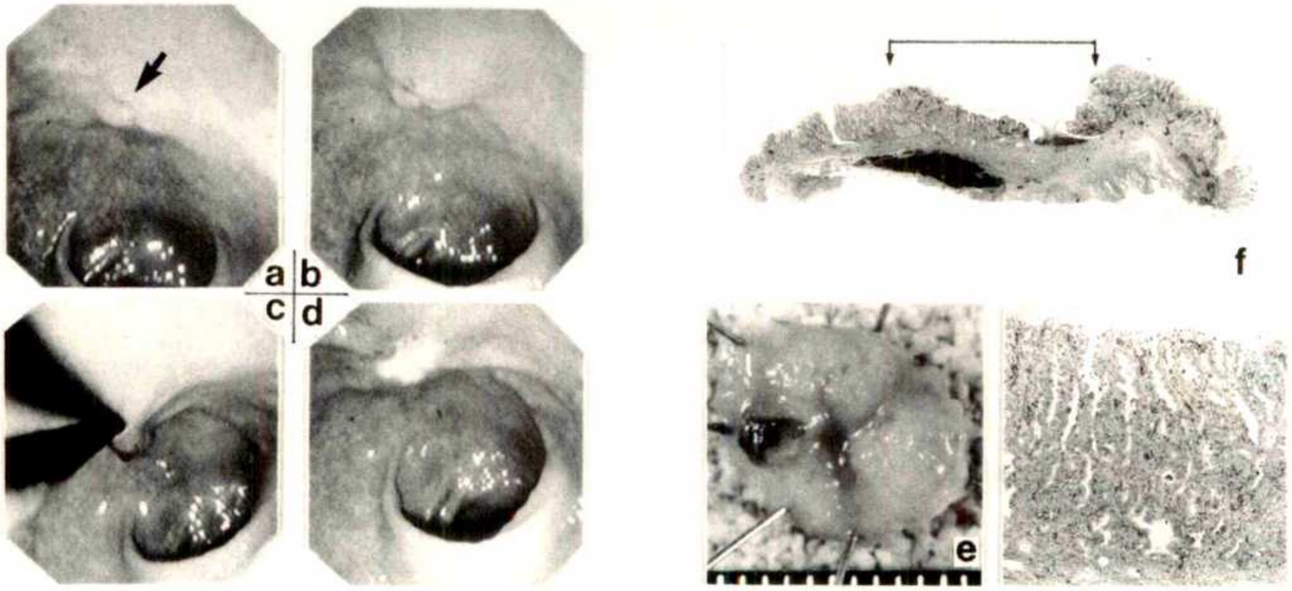

Figure 1 *Endoscopic 'strip-off' resection.* **a** *A small depressed lesion (arrow) is seen in the antrum.* **b** *An injection of saline into the submucosal layer (2 ml in this case) elevated the mucosal lesion.* **c** *The wire loop holds the tumour and surrounding mucosa.* **d** *Resection using high frequency electric current, without bleeding.* **e** *The resected specimen.* **f** *The microscopic view of the specimen. An adenocarcinoma can be seen between the arrows. No invasion of the muscularis mucosa was observed*

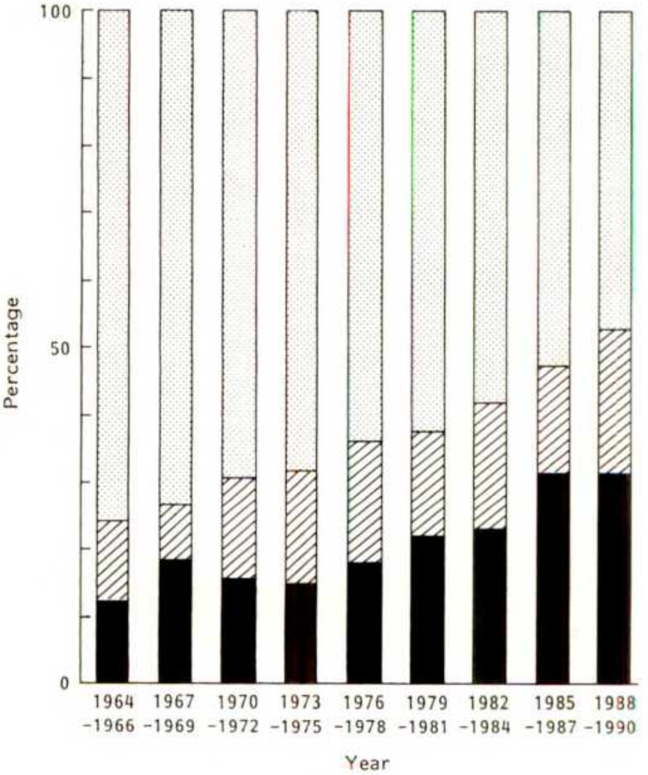

Figure 2 *Increasing proportion of early gastric cancers resected between 1964 and 1990.* ■, *Mucosal;* ▨, *submucosal;* □, *advanced gastric cancers*

diameter was 2 cm or less, node involvement was found in only six cases (*Table 4*). Five of these six were SM-carcinomas.

Macroscopic type

In macroscopically reclassifying lesions into the elevated or depressed group (*Table 5*), no significant difference in node involvement was found between them.

Intramural ulcer or ulcer scar

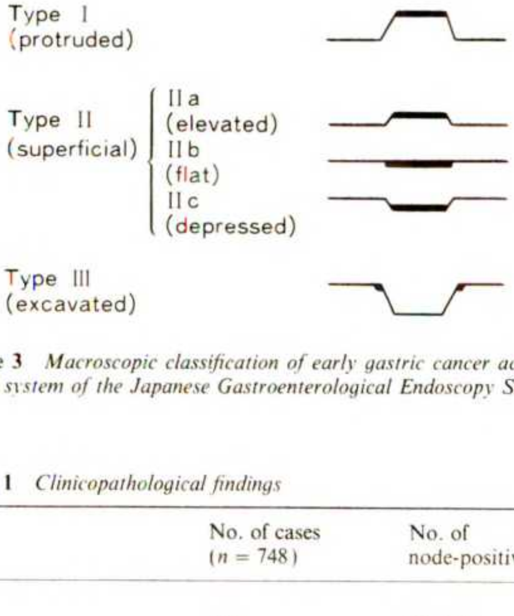

Figure 3 *Macroscopic classification of early gastric cancer according to the system of the Japanese Gastroenterological Endoscopy Society*

Table 1 *Clinicopathological findings*

	No. of cases (n = 748)	No. of node-positive cases
Sex		
M	527	51 (9·7)
F	221	26 (11·8)
Depth of invasion		
Mucosa	426	14 (3·3)
Submucosa	322	63 (19·6)
Macroscopic type*		
Elevated	137	16 (11·7)
Depressed	600	61 (10·2)
Flat (IIb)	11	0 (0·0)
Histological type		
Differentiated	471	51 (10·8)
Undifferentiated	277	26 (9·4)

Values in parentheses are percentages. *Details in *Table 5*

Fold convergence was frequently observed around depressed type M-carcinomas, in which histological examination revealed submucosal fibrosis due mostly to intramural ulcers or ulcer scars. A breakdown of the muscularis mucosa by intramural ulcer or ulcer scar was recognized in 211 (63 per cent) of 336 depressed type M-carcinomas. Twelve of the 14 M-carcinomas

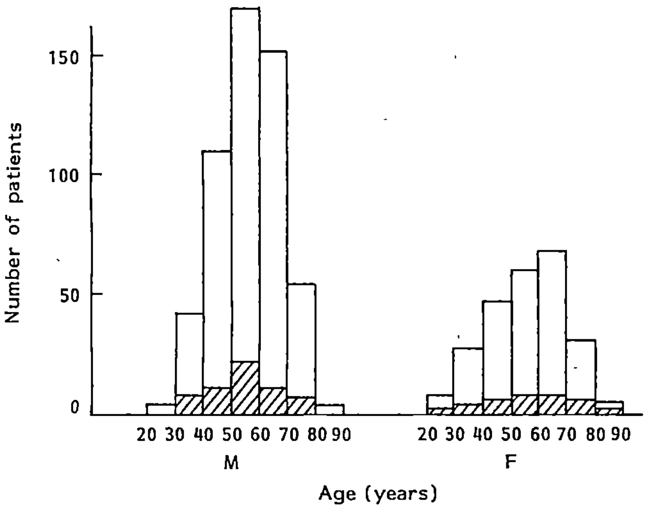

Figure 4 *Age and sex distribution of patients with early gastric cancer. Positive nodes (▨) were seen in about 10 per cent of all groups*

Table 2 *Patients with mucosal carcinomas with positive nodes (14 cases)*

Sex	Age (years)	Macroscopic type	Diameter (cm)	Histological type	Intramural ulcer or scar
M	55	IIc + III	1·8	D	+
M	36	IIc + III	2·4	U	+
F	76	IIc	2·9	U	+
M	41	IIc	3·0	U	–
F	48	IIc + III	5·0	D	+
F	53	I + IIa	5·5	D	–
M	73	IIc	5·5	D	+
F	27	IIc	6·3	D	+
M	39	IIc	6·5	U	+
F	51	IIc + IIa	7·3	D	+
F	41	IIc	7·5	U	+
M	33	IIc + III	8·5	U	+
M	53	IIc + IIa	10·0	U	+
M	43	IIc + III	11·0	D	+

D, differentiated adenocarcinoma; U, undifferentiated adenocarcinoma

Table 3 *Tumour size and node involvement with depth of invasion*

	Tumour diameter (cm)		
	Node positive	Node negative	*P**
Depth of invasion			
Mucosa	5·9(2·8)	3·0(2·3)	<0·001
Submucosa	5·1(2·9)	3·8(2·2)	<0·005

Values are mean(s.d.). *Mann–Whitney *U* test

Table 4 *Node involvement and tumour diameter*

	No. of cases	No. of node-positive cases
Tumour diameter (cm)		
≤2·0	239	6 (2·5)
2·1–4·9	329	32 (9·7)
≥5·0	180	39 (21·7)

Values in parentheses are percentages. $P < 0.001$ (χ^2 test)

with positive nodes were of the depressed type with intramural ulcer or ulcer scar (*Table 2*).

Histological type

Table 5 *Macroscopic classification into elevated or depressed group*

Elevated group	
	I, IIa and other predominantly elevated lesions such as I + IIa or IIa + IIc
Depressed group	
	IIc, III and other predominantly depressed lesions such as IIc + III or IIc + IIa

There was no significant difference in node involvement between differentiated and undifferentiated carcinomas. This was true at each depth of invasion.

Number of positive nodes

The mean number of positive nodes in the 14 M-carcinomas was 1·6, while that of the 63 SM-carcinomas was 2·8. Most of the positive nodes were found in the perigastric region adjacent to the tumour but in 15 patients (19 per cent; two mucosal, 13 submucosal), positive nodes were detected around the coeliac and/or the common hepatic arteries.

Discussion

Japanese surgeons routinely perform lymphadenectomy in patients with early gastric cancer, hoping to resect completely all malignant foci[9]. This approach is reasonable as positive nodes can be found around the coeliac artery in those with early cancers. Lymph node dissection could have been omitted in many cases, however. The absence or presence of lymph node metastasis cannot be correctly diagnosed during surgery. The accuracy of intraoperative macroscopic diagnosis is low (12 per cent) and the number of positive nodes is too small to be accurately sampled for frozen section examination. To modify the strategy of node dissection it is essential to establish criteria for preoperative selection of patients in whom the possibility of node involvement is zero.

In this study the overall frequency of node involvement was 10·3 per cent and only depth of invasion and tumour size correlated significantly with lymph node metastasis.

Positive nodes were found in 19·6 per cent of SM-carcinomas, but in only 3·3 per cent of M-carcinomas. This is readily understandable because the submucosal layer is rich in lymphatic capillaries while they are virtually absent from the mucosal layer. Node involvement in M-carcinoma was exceptional and should be evaluated further. Only 14 patients with M-carcinomas had positive nodes. Twelve tumours were of the depressed type, containing an ulcer or ulcer scar with converging folds, and one was the large (5·5 cm in diameter) elevated type. The existence of intramural ulcer or ulcer scar means breakdown of the muscularis mucosa, raising the possibility that preceding malignant invasion into the submucosa had already occurred.

Lymph node metastases were extremely rare among tumours of 2 cm or less in diameter. Five of six node-positive tumours in this diameter range were SM-carcinomas. The smallest M-carcinoma with positive nodes was 1·8 cm and contained an ulcer penetrating into the muscularis propria layer.

From these results and other reports[7,10] tumours which satisfy the following criteria are unlikely to metastasize to lymph nodes and may be suitable for local resection: (1) confined to the mucosa; (2) less than 1·5 cm in diameter; (3) macroscopically elevated; (4) macroscopically depressed, without intramural ulcers or ulcer scars (endoscopically no fold convergence); and (5) histological differentiation (undifferentiated carcinomas often show diffuse, ill-defined superficial growth). Criteria 2–5 can be verified at endoscopy with biopsy. Criterion 1, which is the most crucial factor for node involvement, remains the most difficult to assess. Routine endoscopy or endoscopic ultrasonography cannot estimate the depth of invasion[11] and histological examination of a whole tumour specimen is necessary to confirm that the tumour is confined to the mucosa.

The technique demonstrated (*Figure 1*), a modified endoscopic polypectomy[6], is appropriate for this purpose because the specimens it provides include the submucosal layer. The cut margin and depth of tumour invasion can be verified histologically.

This method is currently being used in patients at high operative risk, such as those with severe heart or liver disease. Based on the results of this study it may be possible to extend the procedure to other patient groups. These early lesions are rare and the indications should be carefully determined as the results of routine surgery are satisfactory. Follow-up endoscopy is indispensable because synchronous or metachronous cancer arising in the same stomach is not uncommon. The benefits of non-surgical treatment are immense and the establishment of appropriate criteria and techniques is highly desirable.

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Predictors of lymph node metastasis in early gastric cancer

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Data were analysed on 396 patients with early gastric cancer who underwent resection in this department; special reference was made to lymph node metastasis. Metastases were present in the dissected lymph nodes of 47 patients (11·9 per cent). The survival rate for patients with metastasis to lymph nodes was lower than for those without such metastasis ($P < 0{\cdot}05$)*. Lymph node metastasis was associated with larger tumour, a higher incidence of submucosal invasion, a higher rate of lymphatic vessel involvement, an advanced stage of disease and a non-curative resection rate of 6·4 per cent. Multivariate analysis showed that the independent risk factors for lymph node metastasis in patients with early gastric cancer were large tumour size, lymphatic vessel involvement and invasion into the submucosal layer. In patients with these risk factors, lymph node dissection and postoperative adjuvant therapy should be performed in an attempt to prevent recurrence in the form of lymph node metastasis.*

Early gastric cancer is defined as a lesion in which the depth of invasion is limited to the mucosa or mucosa and submucosa, regardless of whether or not regional lymph node metastasis is evident on histological examination[1]. With emphasis on early diagnosis, detection of an early gastric cancer and consequent longer survival are now common[2]. The lymphatic system has an important role in the spread of gastric cancer[3,4] and the incidence of lymph node metastasis varies from 7 to 18 per cent[5,6]. The 10-year survival rate of patients with early gastric cancer and no lymph node involvement is 82–97 per cent, but the rate is less favourable (57–87 per cent) when lymph nodes are involved. This study attempted to determine the type of early gastric cancer which tends to metastasize. The influence of independent clinical and pathological variables on metastasis was determined by logistic regression analysis[7–9].

Patients and methods

Patients

From 1965 to 1985, 396 Japanese patients with early gastric cancer and no evidence of any other malignancy underwent curative gastric resection in this department. Of these, 349 (88·1 per cent) did not have lymph node metastasis. Early gastric cancer occurred in patients with a mean(s.d.) age of 57·7(12·3) years for those without lymph node metastasis, and 58·3(11·6) years for those with lymph node metastasis. The male:female ratio was 2:1. Pathological diagnosis and classification of resected gastric cancer tissue were carried out according to the general rules for the gastric cancer study in surgery and pathology in Japan[1]

Statistical analysis

The BMDP statistical package program (BMDP Statistical Software, Los Angeles, California, USA) for the IBM 4381 mainframe computer (Armonk, New York, USA) was used for all analyses[10]. The BMDP P4F and P3S programs were used for the χ^2 and Mann–Whitney tests to compare data on patients without lymph node metastasis with those on patients with lymph node metastasis. The BMDP P1L program was used to analyse survival by the Kaplan–Meier method and the generalized Wilcoxon test was used to test for equality of the survival curves The BMDP PLR program was used for simultaneous multivariate adjustment of each covariate, using a backward stepwise logistic regression analysis[7–9] In this analysis, age and tumour size were included as continuous variables. The accepted level of significance was $P < 0{\cdot}05$.

Results

Clinicopathological factors

Table 1 shows clinicopathological data on the 349 patients without and the 47 with lymph node metastasis who underwent gastric resection. These groups differed significantly with respect to tumour size, depth of invasion, lymphatic involvement by the primary tumour and operative curability. In gastric cancer with lymph node metastasis, the primary tumour tended to be larger and the incidence of submucosal invasion and lymphatic involvement was higher. Lymph node metastasis was present in one patient with a tumour <2·0 cm in size. This tumour was of the depressed type (IIc) and invaded the submucosa. An advanced stage of disease was more common in patients with lymph node metastasis and three of these 47 patients did not have a curative resection (one with incomplete lymph node dissection and two with cancer infiltration at the resected margin).

Risk factors

All of the factors listed in *Table 1* were examined by logistic regression analysis. The independent risk factors for lymph node metastasis were found to be larger tumour size, submucosal invasion and lymphatic vessel involvement (*Table 2*).

Survival rates

At the time of analysis, the median follow-up for the 262 survivors was 10·6 years. Of the 134 deaths, 33 were related to recurrence of gastric cancer, 24 were due to another malignancy and 77 to another disease or an accident. Deaths not from gastric cancer were considered as lost to follow-up as of time of death for the statistical analysis of cumulative survival rate.

The postoperative survival curve for patients without lymph node metastasis was compared with that obtained for those with lymph node metastasis (*Figure 1*). The 10-year survival rates were 92·0 per cent for those without lymph node metastasis and 84·5 per cent for those with lymph node metastasis, with a statistically significant difference ($P < 0{\cdot}05$).

Discussion

Gastric cancer is common in Japan[2,11,12] and some authors consider that social, dietary and infectious factors are involved[13–15]. The overall survival rate of patients with gastric

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Table 1 *Clinicopathological factors in patients with early gastric cancer with and without lymph node metastasis*

Factor	Without lymph node metastasis ($n = 349$)	With lymph node metastasis ($n = 47$)	P
Mean(s.d.) age (years)	57·7(12·3)	58·3(11·6)	n.s.
Sex			
M	238 (68·2)	30 (63·8)	n.s.
F	111 (31·8)	17 (36·2)	
Macroscopic appearance			
Protruded type	40 (13·5)	3 (7·3)	n.s.
Depressed type	257 (86·5)	38 (92·7)	
Unknown*	52	6	
Maximum mean(s.d.) tumour diameter (cm)	3·6(2·2)	4·8(2·3)	<0·01
Tumour diameter (cm)			
<2	80 (22·9)	1 (2·1)	<0·01
2–3	84 (24·1)	8 (17·0)	
>3	185 (53·0)	38 (80·9)	
Tumour location			
Upper	41 (11·8)	2 (4·3)	n.s.
Middle	154 (44·1)	26 (55·3)	
Lower	154 (44·1)	19 (40·4)	
Stage			
I	349 (100)	2 (4·3)	<0·01
II	0 (0)	31 (66·0)	
III	0 (0)	13 (27·7)	
IV	0 (0)	1 (2·1)	
Histology			
Differentiated	215 (61·6)	28 (59·6)	n.s.
Undifferentiated	134 (38·4)	19 (40·4)	
Histological depth of invasion			
Mucosa	177 (50·7)	6 (12·8)	<0·01
Submucosa	172 (49·3)	41 (87·2)	
Lymphatic involvement			
No invasion	260 (90·9)	20 (52·6)	<0·01
Minimal invasion	22 (7·7)	11 (28·9)	
Intermediate invasion	3 (1·0)	4 (10·5)	
Severe invasion	1 (0·3)	3 (7·9)	
Unknown*	63	9	
Vascular involvement			
No invasion	271 (97·5)	33 (94·3)	n.s.
Minimal invasion	7 (2·5)	2 (5·7)	
Unknown*	71	12	
Histological growth pattern			
Expansive	127 (49·8)	15 (37·5)	n.s.
Intermediate	85 (33·3)	18 (45·0)	
Infiltrative	43 (16·9)	7 (17·5)	
Unknown*	94	7	
Gastric resection			
Partial	305 (87·4)	43 (91·5)	n.s.
Total	44 (12·6)	4 (8·5)	
Lymph node dissection			
R_1	58 (16·6)	6 (12·8)	n.s.
R_2	184 (52·7)	21 (44·7)	
R_3	107 (30·7)	20 (42·6)	
Curability			
Curative	345 (98·9)	44 (93·6)	<0·05
Non-curative	4 (1·1)	3 (6·4)	

Values in parentheses are percentages unless stated otherwise. *Unknown cases were excluded from statistical analysis; n.s., not significant

Table 2 *Logistic regression analysis for variables associated with lymph node metastasis in early gastric cancer*

Explanatory variable (observed value)	P	Regression coefficient
Depth of invasion (mucosa, submucosa)	<0·01	2·80
Lymphatic vessel involvement (none, present)	<0·01	2·12
Tumour size (per centimetre)	<0·01	1·32

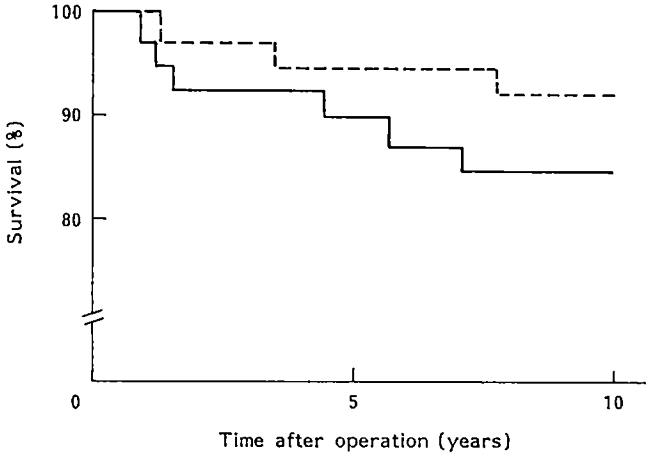

Figure 1 *Survival curves for patients undergoing resection for gastric cancer with (——) and without (----) lymph node metastasis*

cancer in Japan is often 50 per cent or higher because of the high incidence of early stage disease.

The most important factor related to the prognosis of early gastric cancer appears to be the presence or absence of lymph node metastasis; liver metastasis or peritoneal dissemination is extremely rare in patients with early gastric cancer[5,16]. The 10-year survival rate is low in patients with positive nodes. This study compares the clinicopathological features of patients with early gastric cancer with lymph node metastasis with those of patients without lymph node metastasis.

Habu *et al.*[5] found that metastasis was significantly more frequent in the combined type of early gastric cancer such as IIa + IIc, and from large tumours which invade the submucosa. Boku *et al.*[17] reported that lymph node metastasis is more frequent in the protruded-type cancer with a diameter >3 cm and invasion into the submucosa, and in tumours located in the lower third of the stomach. Hioki *et al.*[4] found that lymph node metastases are common in patients with submucosal or elevated early gastric cancer, particularly if the lesions are ⩾4 cm in diameter and are poorly differentiated with vascular invasion. Studies on nodal involvement in early gastric cancer have shown that lymph nodes are not involved in any polypoid mucosal cancer which measures <2·0 cm in diameter[6,18], and that conservative surgery can be performed on such patients. In this study, lymph node metastasis was noted in only one patient with a tumour <2·0 cm in diameter, which was of the depressed type and which had invaded the submucosa.

Analysis of risk factors by multivariate regression models provides more information pertinent to decision-making processes than does simple statistical analysis[9]. Independent risk factors for the occurrence of lymph node metastasis are large tumour size, submucosal invasion, and lymphatic involvement by tumour cells. The present findings may aid in determining how extensive lymph node dissection should be in any individual case of early gastric cancer. Tumour size can be determined for all cases and the depth of invasion estimated before operation in more than 80 per cent of cases[19,20]. By combining these data, the accuracy of preoperative diagnosis of lymph node metastasis should be increased.

Recurrence in the lymph nodes has been attributed to an inadequate lymph node dissection[16] When tumours are large and invasive, prophylactic lymph node dissection is essential; this procedure does not contribute to postoperative mortality[21]. In patients with all of these risk factors close follow-up and careful planning of postoperative adjuvant therapy[22,23] are necessary to avoid recurrence, even when a 'curative' resection is performed.

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Quality of life after gastrectomy in patients with carcinoma of the stomach

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One hundred and fifty patients without recurrence of disease after R_2 gastrectomy for carcinoma of the stomach were interviewed to determine their quality of life after surgery. Patients ate less and weighed less but most appeared to be well adjusted and had an optimistic attitude regarding their physical state. There was no evidence of a diminished quality of life in those who had undergone distal partial gastrectomy. These patients had a higher overall food tolerance, body-weight and performance status compared with those treated by total gastrectomy. Considering the satisfactory outcome and the sustained quality of life, radical R_2 gastrectomy may be the treatment of choice for carcinoma of the stomach.

Extensive lymph node dissection and combined resection of involved organs gives a significant prolongation of survival for patients with gastric cancer treated by curative surgery[1-7] Such *en bloc* operations have a greater margin of safety, the operative mortality rate being less than 5 per cent[3-7]. Since patients with carcinoma of the stomach are surviving for longer periods of time more attention should be directed to the relief of symptoms and to the quality of life.

The quality of life of patients who have undergone surgery for carcinoma of the oesophagus[8,9] or colon[10-12] or repair of abdominal aortic aneurysm[13] has been discussed. Little is known of the results following radical surgery for gastric cancer.

In this study, food tolerance, body-weight and performance status were determined in patients with no recurrence of disease after R_2 gastrectomy for carcinoma. The objective of the study was to clarify whether the operative procedure was justified in terms of the quality of life in such patients after operation.

Patients and methods

Patients

One hundred and fifty patients with carcinoma of the stomach who had undergone R_2 gastrectomy between 1969 and 1987 were studied All were in good clinical condition without recurrence of disease when the survey was carried out in 1989 Clinical data are shown in *Table 1*; 83 patients had undergone distal partial gastrectomy and 67 total gastrectomy.

Table 1 *Patient details*

	No of patients
Age (years)	
≤59	89
≥60	61
Sex ratio (M.F)	97·53
Type of surgery	
Distal gastrectomy	
Billroth I	43
Billroth II	40
Total gastrectomy	
With splenectomy	34
Without splenectomy	33
Stage of disease*	
I	67
II	27
III	46
IV	10
Time after operation (years)	
1–3	33
3–6	32
6–10	31
>10	54
Total	150

*Japanese staging system

Surgical procedures

R_2 gastrectomy had been performed as described by the Japanese Research Society for Gastric Cancer[1] The entire greater omentum, superior leaf of the mesocolon, pancreatic capsule and lesser omentum had been removed *en bloc* with the stomach When the tumour had involved the middle or lower third of the stomach, a distal partial gastrectomy had been performed with dissection of the perigastric nodes along lesser and greater curvatures and those in the right paracardial, suprapyloric and infrapyloric regions. Extragastric nodes, such as those along the left gastric, splenic, coeliac and common hepatic arteries, had also been dissected The left gastric artery had been ligated and divided at its origin When the tumour had been located in the upper third of the stomach total gastrectomy had been carried out. Lymphadenectomy in the left paracardial region had also been performed. In general, splenectomy had not proven necessary in patients with early gastric carcinoma. Reconstructive surgery had used an intestinal loop brought up to the lower oesophagus through an antecolic route. Oesophagojejunostomy had been performed in an end-to-side fashion An enteroenterostomy had been constructed about 35–40 cm distant from the oesophagojejunostomy.

Analysis

The 16-item survey examined food tolerance, body-weight, performance status and was adapted objectively to assess the quality of life, in a qualitative fashion (*Table 2*) The Eastern Cooperative Oncology Group performance status scale[14] was used to determine the level of activity of each patient Each survey was performed by the same interviewer Scores were assigned by the questioner for each of the items to express quantitatively the degree of physical and social well-being The lower the score, the higher the discriminant power to indicate a good quality of life Average scores were calculated for the response to each question and used as the index for the quality of life Results are expressed as mean(s.d) Statistical analysis was performed using the Mann–Whitney rank sum test

Results

Results with regard to food tolerance, body-weight and performance status are shown in *Table 3* The majority of patients were consuming a normal diet after operation, but more than 50 per cent of patients were unable to tolerate the same volume of food About half the patients had some loss of appetite Eleven of 33 patients had lost over 10 kg within 3 years of surgery but this incidence decreased to ten of 54 10 years after operation. Postoperative performance status

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Table 2 *Questions and scoring for quality of life variables for patients who had undergone R_2 gastrectomy*

Question	Answers	Scoring
1. How many times do you eat per day?	2–3 times	(1)
	4–5 times	(2)
	⩾6 times	(3)
2. How long do you take to eat?	<20 min	(1)
	20–30 min	(2)
	>30 min	(3)
3. What is the consistency of the food?	Normal	(1)
	Soft	(2)
	Liquid	(3)
4. How large are the portions compared with before your illness?	Increased	(1)
	Unchanged	(2)
	2/3 pre-disease	(3)
	1/2 pre-disease	(4)
	1/3 pre-disease	(5)
5. What is your postoperative body-weight?	Increased	(1)
	Unchanged	(2)
	<5 kg loss	(3)
	5–10 kg loss	(4)
	>10 kg loss	(5)
6. How is your appetite?	Good	(1)
	Fair	(2)
	Poor	(3)
7. Do you have problems swallowing?	Never	(1)
	Sometimes	(2)
	Often	(3)
8. Do you ever have diarrhoea?	Never	(1)
	Sometimes	(2)
	Often	(3)
9. Do you ever have heartburn?	Never	(1)
	Sometimes	(2)
	Often	(3)
10. Do you ever feel uncomfortable after eating?	Never	(1)
	Sometimes	(2)
	Often	(3)
11. Do you ever have abdominal pain?	Never	(1)
	Sometimes	(2)
	Often	(3)
12. Do you ever vomit?	Never	(1)
	Sometimes	(2)
	Often	(3)
13. Do you tire easily?	Never	(1)
	Sometimes	(2)
	Often	(3)
14. Do you ever have dizziness?	Never	(1)
	Sometimes	(2)
	Often	(3)
15. Have you ever seen a doctor because of intestinal obstruction?	No	(1)
	Yes, but not surgically treated	(2)
	Yes, surgically treated	(3)
16. What is your level of activity (performance status)?		
PS 0: Fully active, able to carry on all pre-disease performance without restrictions.		(0)
PS 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature: light housework, office work.		(1)
PS 2: Ambulatory and capable of total self-care but unable to carry out any work activities; up and about more than 50 per cent of waking hours.		(2)
PS 3: Capable of only limited self-care, confined to bed or chair more than 50 per cent of waking hours.		(3)
PS 4: Completely disabled, incapable of any self-care, totally confined to bed or chair.		(4)

Table 3 *Results of interview*

	Time after operation (years)			
	1–3 ($n = 33$)	3–6 ($n = 32$)	6–10 ($n = 31$)	>10 ($n = 54$)
Consistency of food				
Normal	28	28	24	47
Soft	1	3	5	5
Liquid	4	1	2	2
Volume of food*				
Increased	2	2	0	4
Unchanged	7	12	13	17
Decreased	24	18	18	33
Appetite				
Good	4	2	1	1
Fair	15	11	9	24
Poor	14	19	21	29
Body-weight*				
Increased	4	0	4	4
Unchanged	1	5	4	6
Decreased				
<5 kg	7	7	3	12
5–10 kg	10	11	12	22
>10 kg	11	9	8	10
Performance status				
0	8	10	14	23
1	16	17	12	21
2	7	4	3	9
3	2	0	1	1
4	0	1	1	0

*Compared with the weight before disease

Table 4 *Score for each question according to age*

	Age at operation (years)		
Question no.	⩽59 ($n = 89$)	⩾60 ($n = 61$)	P*
1	1·31(0·49)	1·36(0·57)	0·80
2	1·48(0·62)	1·63(0·73)	0·22
3	1·13(0·43)	1·32(0·65)	<0·05
4	2·88(1·00)	2·95(1·03)	0·62
5	3·73(1·42)	3·70(1·29)	0·65
6	2·48(0·58)	2·52(0·62)	0·56
7	1·58(0·72)	1·59(0·69)	0·88
8	1·46(0·54)	1·34(0·54)	0·14
9	1·50(0·67)	1·37(0·61)	0·23
10	1·56(0·70)	1·37(0·52)	0·17
11	1·26(0·53)	1·21(0·45)	0·63
12	1·16(0·43)	1·16(0·41)	0·99
13	1·51(0·67)	1·39(0·58)	0·30
14	1·39(0·61)	1·29(0·58)	0·24
15	1·30(0·59)	1·19(0·47)	0·27
16	0·60(0·79)	1·27(0·79)	<0·001

Values are mean(s.d.). *Mann–Whitney rank sum test

revealed 24 of 33 patients with grades 0 or 1 within 3 years of operation but the performance status grade gradually improved and a majority were classed as grades 0 or 1 at 10 years.

Table 4 shows the results of the self-evaluation of life function scale according to the patient's age. Those aged less than 60 years had favourable scores with regard to the consistency of food eaten and performance status, compared with those over 60 years. There were no significant differences with regard to other items between the two groups. Variations in the quality of life according to the type of surgery are detailed in *Table 5*. Patients who had undergone partial gastrectomy showed favourable scores with regard to food tolerance, body-weight and performance status compared with findings in the total gastrectomy group.

Table 5 *Score for each question according to the type of gastrectomy*

Question no.	Type of gastrectomy Distal ($n = 83$)	 Total ($n = 67$)	P*
1	1·19(0·45)	1·50(0·56)	<0·001
2	1·38(0·60)	1·74(0·70)	<0·001
3	1·04(0·21)	1·41(0·72)	<0·001
4	2·61(0·85)	3·28(1·08)	<0·001
5	3·43(1·24)	4·07(1·43)	<0·01
6	2·57(0·52)	2·40(0·67)	0·15
7	1·33(0·59)	1·89(0·72)	<0·001
8	1·38(0·53)	1·44(0·55)	0·48
9	1·36(0·59)	1·56(0·70)	<0·05
10	1·31(0·53)	1·70(0·69)	<0·001
11	1·13(0·37)	1·38(0·60)	<0·01
12	1·10(0·31)	1·23(0·52)	0·12
13	1·34(0·59)	1·61(0·67)	<0·01
14	1·21(0·54)	1·52(0·63)	<0·001
15	1·25(0·58)	1·26(0·51)	0·49
16	0·66(0·68)	1·14(0·97)	<0·01

Values are mean(s.d.). *Mann–Whitney rank sum test

Discussion

Surgery may have a long-lasting influence on the quality of life and sense of well-being, although these are hard to quantify accurately. Attention has instead been directed to the statistics of morbidity, mortality and survival time. To obtain a more comprehensive measure of the results of R_2 gastrectomy, attention was directed towards assessment of the functional outcome and the extent to which patients were able to return to a normal preoperative lifestyle.

Although it was difficult to regain the lost weight, disturbances in performance status were considerably improved 3 years after surgery. About 80 per cent of the patients were able to work and the majority of those treated by R_2 gastrectomy enjoy good quality of life, if there is no recurrence. There was a distinct difference in scores (food tolerance, body-weight and performance status) between patients who had undergone total gastrectomy and those treated by distal partial gastrectomy; total gastrectomy is disabling. For patients who had undergone distal partial gastrectomy, there was a prompt return to the preoperative lifestyle. Most patients' performance status was either 0 or 1 and the performance status was very good in both groups. Significant changes occurred with questions 4 (food tolerance) and 5 (body-weight).

The best surgical procedure for carcinoma of the lower two-thirds of the stomach is controversial. Some surgeons favour total gastrectomy 'de principle' as a radical treatment. Shui *et al.*[2] recommended a radical total gastrectomy as the procedure of choice for carcinoma of the mid-stomach. Some believe partial gastrectomy still represents the standard reference operation for gastric cancer provided that a safe proximal resection margin is guaranteed[15]. Mitsudomi *et al.*[16] reported that survival after total gastrectomy does not exceed that after partial gastrectomy when allowance is made for histological stage. In a multivariate discriminate analysis, the type of surgery proved to be a major independent risk factor related to postoperative complications. Increased morbidity was related to wide resectional procedures such as total gastrectomy[17]. These studies did not include data on the postoperative quality of life.

This study shows that the quality of life is usually better after partial gastrectomy than after total gastrectomy. Long-term palliation and control of the disease is feasible with distal R_2 partial gastrectomy for patients with carcinoma of the lower two-thirds of the stomach. These findings on the quality of life after operation suggest that radical R_2 gastrectomy, if practical, may be the treatment of choice for a carcinoma of the stomach. Total gastrectomy should probably be limited to cases of carcinoma of the upper third of the stomach.

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Serum electrolytes and capillary blood gases in the management of hypertrophic pyloric stenosis

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The purpose of this study was to assess whether the concentration of serum chloride and other variables, namely serum sodium, potassium and bicarbonate, can be used to predict metabolic acid–base status in infants with hypertrophic pyloric stenosis (HPS) and to assess whether such a prediction is influenced by the state of hydration. One hundred and sixty-three infants with HPS who had at least one set of serum electrolyte and capillary blood gas estimations performed after admission were studied retrospectively. A further 25 infants who had their electrolyte and blood gases measured after at least 12 h of rehydration and correction of the serum sodium and chloride abnormalities were studied prospectively. Stepwise multiple regression analysis, using standard bicarbonate as the dependent variable, revealed serum chloride concentration to be the most powerful independent predictor of standard bicarbonate level ($r = -0{\cdot}69$, $P < 0{\cdot}0001$)*. Other variables did not improve the correlation significantly. In the retrospective study of untreated patients, the calculation of a 90 per cent prediction interval for the model indicated that if the serum chloride level is less than 96 mmol/l, one could be 95 per cent confident (one tail) that the patient was alkalaemic. To be 95 per cent confident that the patient was not alkalaemic, the serum chloride level would have to be greater than 121 mmol/l. The prospective study found that following rehydration a serum chloride level greater than or equal to 106 mmol/l more accurately predicted absence of alkalaemia. We conclude that predictability of acid–base status from measurement of serum chloride depends on the state of hydration of the patient.*

Metabolic alkalosis is the major biochemical abnormality in infants presenting with hypertrophic pyloric stenosis (HPS)[1,2]. This is mainly a result of loss of chloride and hydrogen ions in the vomitus. Correcting the alkalaemia before general anaesthesia is important to avoid depression of the respiratory centre, carbon dioxide retention and apnoea after operation[3].

Both serum electrolyte and capillary blood gas measurements may be used in the management of infants with HPS. Since the metabolic alkalosis is due mainly to hypochloraemia, it is possible that the degree of alkalosis can be predicted from the serum chloride level. A recent study concluded that serum chloride level is a reliable index of acid–base status both on admission and during correction of alkalaemia[4], and also suggested that if the serum chloride concentration is 106 mmol/l or greater, the incidence of alkalaemia is nil[4].

In the dehydrated infant, the metabolic abnormalities due to external losses are modified by haemoconcentration, and the serum chloride level may be falsely elevated. Therefore, we hypothesized that the relationship between the serum chloride level and acid–base status before operation is dependent on the state of hydration of the patient. The purpose of this study was to ascertain whether the serum chloride level can be used to predict metabolic acid–base status, and to assess whether such a prediction is influenced by the dehydration usually present in patients with HPS at presentation.

Patients and methods

This two-phase study comprised both retrospective and prospective components

Retrospective study

The records of patients who underwent pyloromyotomy for HPS between November 1987 and June 1990 were reviewed retrospectively A set of serum electrolyte and capillary blood gas estimations performed simultaneously after admission was extracted from the records for analysis.

Prospective study

Patients admitted between December 1990 and May 1991 were studied prospectively. Serum electrolyte and blood gas levels, obtained simultaneously after the patient had received intravenous therapy for a minimum of 12 h and the hyponatraemia and hypochloraemia (but not necessarily the acid–base abnormality) had been corrected, were documented for analysis

Definitions

Standard bicarbonate concentration (serum bicarbonate level standardized to a P_{CO_2} of 40 mmHg to correct for the respiratory component) was taken as an accurate indicator of metabolic acid–base status. In this laboratory the normal range for standard bicarbonate is 18–26 mmol/l and for serum chloride it is 95–105 mmol/l

Statistical analysis

Stepwise multiple regression analysis[5] was performed using standard bicarbonate concentration as the dependent variable, and serum chloride, bicarbonate, sodium, potassium and urea levels as independent variables Analysis of the data was performed using the Statistical Package for Social Sciences (SPSS, Chicago, Illinois, USA) Sensitivity and specificity were obtained from contingency tables[6].

Results

Retrospective study

There were 163 patients with a male:female ratio of 5:1 and median age of 5 (range 1–19) weeks. Vomiting had been noted

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Table 1 *Biochemical data and correlations with standard bicarbonate concentration in 163 infants with hypertrophic pyloric stenosis on admission*

	Mean	Range	r*
Standard bicarbonate (mmol/l)	28·80	12·9–44·7	1
pH	7·45	7·24–7·71	−0·52
Serum bicarbonate (mmol/l)	25·99	16–42	0·64
Serum chloride (mmol/l)	103·40	74–117	−0·69
Serum potassium (mmol/l)	4·82	2·6–7·8	−0·46
Serum sodium (mmol/l)	138·46	120–145	−0·26
Serum urea (mmol/l)	2·94	0·5–15	0·34

*Correlation coefficient with standard bicarbonate level as the dependent variable

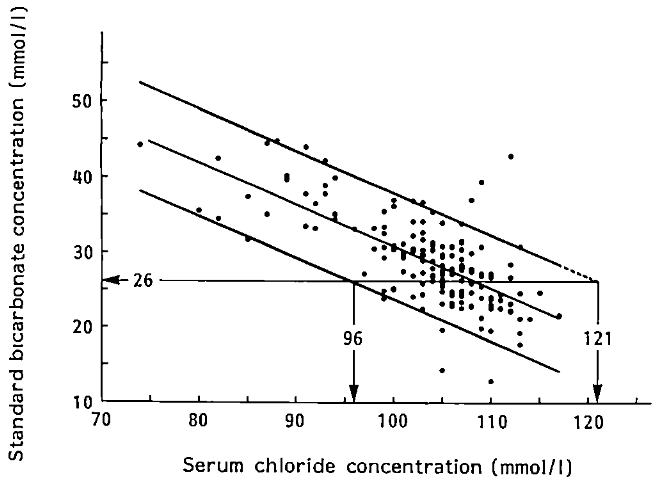

Figure 1 *Linear regression between standard bicarbonate and serum chloride levels on admission, with superimposed 90 per cent prediction interval ----, Line obtained by extrapolation*

Table 2 *Metabolic acid–base status and serum chloride levels in 163 infants with hypertrophic pyloric stenosis on admission*

Serum chloride concentration (mmol/l)	Alkalaemic*	Non-alkalaemic†
<106	74	16
⩾106	33	40
Total	107	56

*Standard bicarbonate level >26 mmol/l; †standard bicarbonate level ⩽26 mmol/l

Table 3 *Biochemical data and correlations with standard bicarbonate concentration in 25 infants with hypertrophic pyloric stenosis after rehydration*

	Mean	Range	r*
Standard bicarbonate (mmol/l)	23·87	17·9–28	1
pH	7·39	7·28–7·48	−0·01
Serum bicarbonate (mmol/l)	22·30	16–29·2	0·56
Serum chloride (mmol/l)	109·40	104–115	−0·42
Serum potassium (mmol/l)	5·57	4·3–7·8	−0·41
Serum sodium (mmol/l)	138·72	135–145	0·08
Blood urea (mmol/l)	1·20	0·2–2·8	0·15

*Correlation coefficient with standard bicarbonate level as the dependent variable

Table 4 *Metabolic acid–base status and serum chloride levels in 25 infants with hypertrophic pyloric stenosis after rehydration*

Serum chloride concentration (mmol/l)	Alkalaemic*	Non-alkalaemic†
<106	1	2
⩾106	1	21
Total	2	23

*Standard bicarbonate level >26 mmol/l, †standard bicarbonate level ⩽26 mmol/l

for a median of 6 (range 1–28) days before admission. The main biochemical data and correlations with standard bicarbonate concentration are given in *Table 1*.

On stepwise multiple regression analysis, the most powerful independent predictor of standard bicarbonate was chloride ($r = -0·69$, $P < 0·0001$; standard bicarbonate (mmol/l) = 86·50 − 0·558 × serum chloride (mmol/l); standard error of the estimate 4·41). The addition of serum bicarbonate, sodium, potassium and urea data to the model did not improve the correlation significantly. The calculation of a 90 per cent prediction interval[7] for the model indicated that if the serum chloride level is less than 96 mmol/l, one could be 95 per cent (one tail) confident that the patient is alkalaemic. Conversely, to be 95 per cent (one tail) confident that a patient is not alkalaemic, the serum chloride level would have to be greater than 121 mmol/l. The observed upper range of our data is 117 mmol/l; the value of 121 mmol/l was obtained by extrapolation (*Figure 1*).

A serum chloride level of 106 mmol/l was found to have a sensitivity of 71 per cent and a specificity of 69 per cent for indicating non-alkalaemia and alkalaemia after admission, i.e. during correction of fluid and electrolyte abnormalities (*Table 2*).

Prospective study

There were 25 patients. The biochemical data and correlations with standard bicarbonate are given in *Table 3*. Standard bicarbonate correlated best with the serum bicarbonate ($r = 0·56$, $P < 0·01$), and rather poorly with chloride ($r = -0·42$, $P = 0·06$). One patient in this group was slightly alkalaemic (standard bicarbonate 27 mmol/l) and had a serum chloride concentration of 107 mmol/l. A serum chloride level of 106 mmol/l had a sensitivity of 91 per cent and the specificity was 50 per cent for indicating non-alkalaemia and alkalaemia (*Table 4*)

Discussion

The biochemical disorder in HPS is so characteristic as to be almost diagnostic in at least 60 per cent of infants[1,2] Apart from the hypochloraemic alkalosis, the disturbance is dominated by sodium depletion due in large part to the renal response[8]. Potassium deficiency exacerbates the alkalosis, but is not the prime cause

In common with other studies, we have adopted standard bicarbonate concentration as the indicator of metabolic acid–base status[1,4]. The serum bicarbonate level has also been used but this does not take into consideration the significant carbon dioxide retention that may occur in an alkalotic infant[3]. Thus, a patient can be significantly alkalotic despite normal serum bicarbonate levels

In their studies of adults with pyloric stenosis, Howe and Le Quesne[8] noted that the most important factor in the development of the metabolic alkalosis was loss of chloride and hydrogen ions due to persistent vomiting, with smaller losses of sodium and potassium ions. This manifests as hypochloraemia and alkalaemia The hypochloraemia is aggravated further because the serum chloride level is lowered to maintain electroneutrality in the face of rising bicarbonate levels[9]. A significant inverse correlation between chloride and standard bicarbonate levels could therefore be expected. However, the large standard error of the estimate and hence wide prediction intervals in the dehydrated infants indicate that, for clinical purposes, serum chloride concentration cannot be used as an accurate predictor of standard bicarbonate level. Although a serum chloride level of less than 96 mmol/l indicates a high probability of alkalosis, to be equally confident that alkalaemia is absent, the serum chloride level would have to be greater than 121 mmol/l in a dehydrated infant.

Goh *et al.*[4], in a recent prospective study, demonstrated that when the serum chloride level is 106 mmol/l or greater the incidence of alkalaemia is nil. They concluded that serum chloride concentration is a reliable index of acid–base status on admission as well as during correction of alkalaemia. From the present observations, however, a serum chloride level of 106 mmol/l or greater cannot be used as a reliable clinical indicator of the absence of alkalaemia in the untreated or partially treated infant. Following hydration and correction of the hypochloraemia and hyponatraemia, the correlation between serum chloride and standard bicarbonate levels was rather poor, due in part to the small number of patients in this group (*Table 3*). There was, however, only one patient who was still alkalaemic with a serum chloride concentration greater than 106 mmol/l. The sensitivity improved from 71 to 91 per cent. Thus, in a hydrated infant, a serum chloride level of more than 106 mmol/l is likely to indicate absence of alkalaemia.

In HPS the main losses of sodium and potassium occur in the urine, in addition to smaller losses from the stomach. The relatively lower extent of correlation of sodium and potassium concentrations with the standard bicarbonate level (*Tables 1* and *3*) indicates that they are not the major ions in the pathogenesis of alkalosis. However, repletion of sodium and potassium is essential for total correction of the metabolic imbalance.

In conclusion, chloride is the major ion in the pathogenesis of metabolic alkalosis associated with HPS. Although there is a significant correlation between serum chloride and standard bicarbonate levels, for clinical purposes standard bicarbonate concentration, and therefore metabolic acid–base status, cannot be reliably predicted from the serum chloride level at the time of admission. Following hydration, however, a serum chloride level of 106 mmol/l or greater predicts more accurately the absence of alkalaemia.

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Thoracoscopic vagotomy: a new use for the laparoscope

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The management of recurrent ulceration after previous gastric operations is a problem for both gastroenterologist and surgeon. Lesions that fail primary surgical treatment are often refractory to medical treatment[1]. The potential complications of recurrent ulceration bring considerable pressure to perform another operation. Further abdominal intervention is associated with considerable morbidity, a reported mortality rate of between 4 and 20 per cent and an ulcer re-recurrence rate of 10–20 per cent[2–4]. Transthoracic vagotomy has been advocated in the management of patients with stomal ulcers or where incomplete vagotomy is suspected, to reduce acid production and to promote ulcer healing[5]. The advantage of such an approach is the opportunity to work in an undisturbed operative field, which makes complete vagotomy more likely to be achieved than by a further abdominal approach[5]. A report of a patient with stomal ulceration who underwent transthoracic vagotomy using an endoscopic technique is presented.

Technique

A 58-year-old man underwent a two-thirds Pólya gastrectomy in 1986 for recurrent haematemesis and melaena from a gastric ulcer. In 1988, he experienced intermittent dyspepsia and at endoscopy was found to have a stomal ulcer He was referred to this hospital in December 1990 after repeated coffee ground vomiting despite H_2-receptor antagonist therapy. He was treated with omeprazole (Losec, Astra, King's Langley, UK) and sucralfate (Ulsanic, Chugai Pharmaceutical, Tokyo, Japan) after further endoscopy demonstrated a 2-cm stomal ulcer and haemorrhagic gastritis. The ulcer showed signs of healing at 6 weeks but the patient was still symptomatic In view of the complication of repeated bleeding it was felt that a truncal vagotomy was indicated. His general condition and previous abdominal surgery suggested transthoracic truncal vagotomy as the appropriate approach, and an endoscopic technique was used.

Under general anaesthesia the patient was placed in the right lateral position. A double lumen endotracheal tube was employed to permit collapse of the left lung. A 10-mm trocar and cannula was inserted through the eighth intercostal space in the posterior axillary line and the laparoscope was introduced. Carbon dioxide insufflation was not used during the procedure Three further 5-mm ports were then established in the sixth, eighth and tenth intercostal spaces, in the mid-axillary line. This allowed dissection of the oesophagus, retraction of the lung and retraction of the diaphragm The inferior pulmonary ligament was freed, and the lung was retracted cephalad. The space behind the pericardiacophrenic junction medial to the aorta was opened and the oesophagus was identified The vagal trunks were identified and clipped with titanium staples, and a portion of each was excised for frozen histological section. The oesophagus could be manipulated using grasping forceps, and the whole circumference could be visualized to identify any further nerve fibres On confirmation of nerve bundles on frozen section in the specimens an intercostal drain was inserted via a porthole and manipulated into position under vision The operation lasted 3 h. The patient was able to eat normally 4 h after operation, and required only one intramuscular injection of analgesic The chest drain was removed on day 2 and he was discharged on the third day after operation. Endoscopy 3 months after the procedure showed that the ulcer had healed.

Discussion

Laparoscopic cholecystectomy demonstrates the principle of using minimally invasive techniques to perform standard surgical procedures. This technique leaves the patient with barely perceptible scars, and allows prompt discharge from hospital and early resumption of work[6]. With the introduction of laparoscopic hernia repair and appendicectomy, the range of endoscopic procedures is increasing[7]. Variations of highly selective vagotomy have been performed laparoscopically[8], but the procedure is tedious and time-consuming.

Open thoracotomy for transthoracic vagotomy may be safer than transabdominal re-exploration of the lower oesophagus. It could not be described as minimally invasive. Operative thoracoscopy is not new; transthoracic endoscopic ablation of the sympathetic chain is one of the standard procedures for hyperhidrosis of the upper limb[9]. Experience with laparoscopic cholecystectomy and considerable oesophageal surgical expertise[10,11] led us to believe that transthoracic endoscopic truncal vagotomy could be performed safely. The oesophagus is identified by working with forceps in an anteromedial direction towards the base of the pericardium at the cardiacophrenic border. Once in the plane of the oesophagus the nerve fibres can easily be isolated. The procedure is less demanding than laparoscopic cholecystecomy. Any surgeon trained and competent in laparoscopic cholecystectomy could perform this procedure endoscopically.

Owing to the minimal distress caused to the patient by the procedure, he was discharged on the third day after operation. The average hospital stay[5] in one series of 47 patients for operative thoracotomy and thoracic vagotomy was 11 days. Abdominal re-exploration may require an even longer hospital stay Where there is no active intra-abdominal complication of recurrent peptic ulceration, which would necessitate an abdominal approach, transthoracic endoscopic ablation of the vagal trunks is justified.

The potential for minimal surgical trauma to patients, often at risk for their general condition, gives this latest vagotomy procedure an obvious advantage. It may find a role in the management of recurrent peptic ulceration, particularly after gastrectomy, where truncal vagotomy would be beneficial.

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Appraisal of percutaneous tracheostomy

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Two commercially available kits have been used to create 25 percutaneous tracheostomies, 20 using the Cook system and five using the Rapitrac system. The operation time and complication rates of these tracheostomies have been compared with those for 16 conventional tracheostomies performed for similar indications. Median operating times were 60 (range 30–105) min for conventional tracheostomy, 15 (range 8–70) min for Cook and 5 (range 3–15) min for Rapitrac systems ($P < 0{\cdot}001$). A significantly higher proportion of patients in the Rapitrac group had complications compared with the other two groups ($P < 0{\cdot}05$). The complication rate for the Cook group compared favourably with that for the conventional tracheostomy group. The Cook system of percutaneous tracheostomy is a simple, rapid and safe alternative to conventional tracheostomy.

Minimally invasive procedures are rapidly transforming many areas of surgical practice and this unit has a major interest in this field. Mini-tracheostomy has been available for a long time but offers only temporary and suboptimal airway access[1]. Percutaneous tracheostomy, a minimally invasive alternative to conventional tracheostomy, was first described by Toye and Weinstein in 1969[2] but it is only recently that kits to create full sized percutaneous tracheostomies have become commercially available. This is an appraisal of percutaneous tracheostomy comparing results with conventional tracheostomy.

Patients and methods

In both the Cook[3] and Schachner[4] systems the trachea is punctured at a chosen level with a needle and cannula and a guidewire is then passed into the trachea using the Seldinger technique[5]. The Ciaglia Cook system (Cook Critical Care, Letchworth, UK) uses graded dilators, 12–36 Fr, which are passed over the guidewire to dilate the track until it is large enough to take a tracheostomy tube (*Figure 1*). The tracheostomy tube is then mounted on one of the dilators and introduced, over the guidewire, into the trachea. Passage of the dilators and tracheostomy tube is facilitated by liberal use of lubricating gel. In the Schachner Rapitrac (Surgitech Medical, Sydney, Australia), a dilatation device, the tracheotome, is passed over the guidewire into the trachea to dilate the track fully in one step. The tracheotome has a bevelled metal cone with a hole through its centre to accommodate the guidewire (*Figure 2a*). Once inserted into the trachea, the handles of the tracheotome are squeezed together causing the metal cone to split into two halves (*Figure 2b*), thus dilating the opening in the trachea. A conventional tracheostomy tube, with a specially designed obturator, is then passed through the tracheal opening. The dilatation instrument and obturator are then removed leaving the tracheostomy tube in place. The Cook kit costs £82.20 and the Rapitrac kit £95.00.

A percutaneous technique has been used to create 25 tracheostomies in 26 consecutive patients referred for tracheostomy between January 1990 and February 1991. The one patient in whom a percutaneous technique was not attempted had marked enlargement of the thyroid isthmus. The indications for tracheostomy were prolonged ventilation, chest injury, to aid weaning off the ventilator and to aid airway suction. All patients were being ventilated on the intensive care unit and were sedated with continuous intravenous infusion of either propofol or midazolam. Informed consent was obtained in all cases from the patient or relatives. Twenty-two procedures were performed on the intensive care unit and in these patients the rate of infusion of propofol or midazolam was increased just before the procedure to ensure adequate sedation for the procedure. The other three procedures were carried out in the operating theatre after other surgery, under general anaesthesia.

After increasing sedation, a sandbag was placed under the shoulders and the neck extended, where this was not contraindicated. The inspired oxygen concentration was increased to 100 per cent and maintained at this level until the end of the procedure. Oxygen saturation was monitored throughout using pulse oximetry. While visualizing the laryngopharynx with a laryngoscope, the cuff of the endotracheal tube

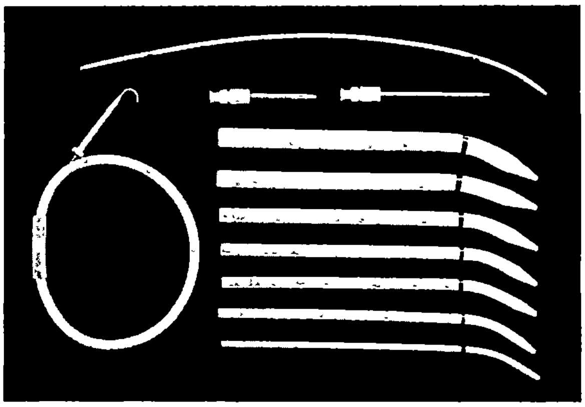

Figure 1 *Cook percutaneous tracheostomy kit. © Department of Medical Illustration, Salford Health Authority*

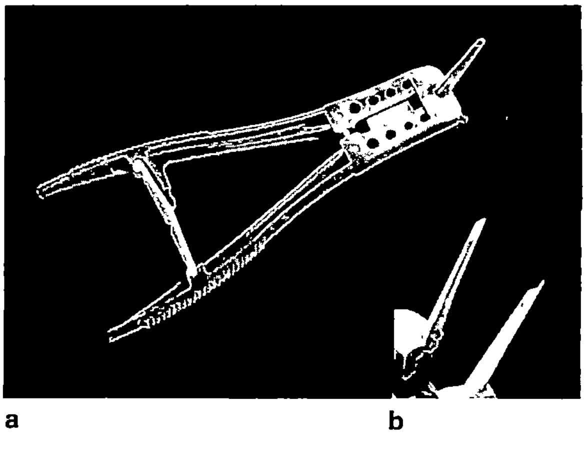

Figure 2 *Rapitrac tracheotome* **a** *closed and* **b** *(inset) opened. © Department of Medical Illustration, Salford Health Authority*

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was deflated and the tube withdrawn so that the cuff was at a level just below the vocal cords. The cuff was then reinflated. Any leak caused by this, or occurring during the procedure, was compensated for by increasing the minute volume of ventilation; this was not necessary in most cases. The cricoid cartilage was identified and the skin and subcutaneous tissues 1·5 cm below it infiltrated with a mixture of 1 per cent lignocaine and 1:200 000 adrenaline, carrying the injection down to the trachea and through into it. If tracheal puncture was obstructed by the endotracheal tube, the tube was withdrawn further to allow free access with the needle into the trachea. The trachea was then fixed with thumb and index finger of one hand and punctured with the needle and cannula at the predetermined level, through a 1-cm (vertical or horizontal) incision in the skin and subcutaneous tissues. The cannula was then advanced in a caudal direction into the trachea. To check that the trachea had been cannulated, air was aspirated using a syringe attached to the cannula. A further check of correct cannula position was made by disconnecting the syringe and listening for the characteristic hissing through the cannula, in time with the ventilatory movements. The guidewire was then passed through the cannula into the trachea and percutaneous tracheostomy performed by one of the two methods described.

Twenty tracheostomies were performed with the Cook system and five with the Rapitrac system. There were 12 adverse factors for tracheostomy present in ten patients (*Table 1*). Results of percutaneous tracheostomy were compared with those of 16 conventional tracheostomies performed by otolaryngologists at this hospital between October 1985 and October 1989. This was a consecutive series and did not include tracheostomies performed as an adjunct to other ear, nose and throat procedures or tracheostomies performed by neurosurgeons or general surgeons. The indications for conventional tracheostomy in these patients were similar to those for percutaneous tracheostomy. All conventional tracheostomies were carried out in the operating theatre under general anaesthesia. The time taken to perform tracheostomy was recorded in both groups as the time from administration of anaesthesia to insertion of the tracheostomy tube.

Table 1 *Adverse factors present in ten of 25 patients undergoing percutaneous tracheostomy*

Adverse factor present	Number
Short fat neck	6
Neck extension contraindicated	3
Coagulopathy	2
Previous thyroid surgery	1
Total	12

Results

Percutaneous tracheostomy was successful in all patients in whom it was attempted. Patient and operative details for Cook, Rapitrac and conventional tracheostomies are shown in *Tables 2, 3* and *4*, respectively. These are summarized for comparison in *Table 5*. The lowest oxygen saturation recorded during percutaneous tracheostomy was 97 per cent occurring in one patient and this did not fall from preoperative levels in any of the other cases. Percutaneous tracheostomy by either system was significantly quicker than conventional tracheostomy ($P < 0{\cdot}001$, Mann–Whitney U test). Of the percutaneous procedures, the Rapitrac was significantly quicker to perform than the Cook ($P < 0{\cdot}05$, Mann–Whitney U test). In patient no. 15 in the Cook group (*Table 2*) the procedure took 70 min because of difficulty in cannulating the trachea as a result of previous thyroid surgery. This was eventually overcome by using a fibreoptic bronchoscope to guide the

Table 2 *Cook percutaneous tracheostomy in 20 patients*

Patient no.	Age (years)	Sex	Diagnosis	Time taken (min)	Tube size (mm)	Adverse factors	Complications
1	44	M	Head injury	12	8	None	None
2	74	M	Pneumonia	15	7·5	None	Minor skin edge bleeding
3	53	F	Pancreatitis	10	8	Short fat neck Coagulopathy	Minor skin edge bleeding
4	69	F	Multiple organ failure secondary to intra-abdominal sepsis	15	8	Short fat neck	None
5	43	M	Multiple organ failure secondary to intra-abdominal sepsis	13	8	None	None
6	67	F	Multiple organ failure secondary to intra-abdominal sepsis	9	7·5	None	None
7	42	M	Multiple organ failure secondary to intra-abdominal sepsis	20	9	None	Minor skin edge bleeding
8	68	M	Flail chest	25	9	None	None
9	51	M	Cervical spinal cord injury	20	9	Cervical cord injury	None
10	53	M	Pneumonia	20	7·5	None	None
11	77	M	Guillain–Barré syndrome	20	8	None	None
12	52	F	Multiple organ failure secondary to pancreatitis	20	8	None	None
13	49	M	Multiple organ failure secondary to intra-abdominal sepsis	12	7·5	Short fat neck	None
14	40	M	Cervical spinal cord injury	21	7·5	Cervical cord injury	None
15	45	F	Head injury	70	8	Previous thyroidectomy	None
16	79	F	Multiple injuries	8	8	Fractured cervical spine	None
17	62	M	Multiple injuries	12	9	Short fat neck Coagulopathy	None
18	77	M	COAD	8	9	Short fat neck	None
19	68	F	COAD	9	8	None	None
20	23	M	Head injury	25	8	None	None

COAD, chronic obstructive airway disease

Table 3 *Rapitrac percutaneous tracheostomy in five patients*

Patient no	Age (years)	Sex	Diagnosis	Time taken (min)	Tube size (mm)	Adverse factors	Complications
1	64	M	Multiple organ failure secondary to intra-abdominal sepsis	5	8	None	Air leak from cuff
2	33	M	Multiple injuries	3	8	None	Air leak from cuff Tracheal stenosis
3	72	F	Multiple organ failure secondary to intra-abdominal sepsis	4	6	None	None
4	61	F	Multiple organ failure secondary to aortic aneurysm repair	14	8	None	Tube misplacement, occlusion, bilateral pneumothorax
5	75	M	Pneumonia	15	8	Short fat neck	Tube misplacement, air leak from cuff

Table 4 *Conventional tracheostomy in 16 patients*

Patient no	Age (years)	Sex	Diagnosis	Time taken (min)	Complications
1	47	F	COAD	50	None
2	44	M	Guillain–Barré syndrome	45	None
3	59	F	Herpes encephalitis	40	Wound infection, tube occlusion, displacement and misplacement
4	67	M	COAD	35	Wound infection
5	44	F	Pancreatitis	80	None
6	63	F	Hereditary motor neuropathy	50	None
7	70	F	COAD	30	None
8	55	M	Guillain–Barré syndrome	105	None
9	51	M	Multiple injuries	60	None
10	32	F	Multiple organ failure, post-partum sepsis	80	None
11	44	M	Intracranial abscess	60	None
12	64	M	COAD	60	None
13	56	F	COAD	55	None
14	54	M	Guillain-Barré syndrome	90	None
15	75	M	COAD	90	None
16	60	M	Guillain–Barré syndrome	80	None

COAD, chronic obstructive airway disease

cannula into the trachea under direct vision This technique has been described by others[6].

The median size of the tracheostomy tube inserted for both percutaneous tracheostomy groups was 8 mm (range 7·5–9 mm for the Cook system and 6–8 mm for the Rapitrac system). The Rapitrac kit comes with an obturator to fit either a 6-mm or 8-mm tube. It was found to be difficult to squeeze an 8-mm tube between the jaws of the tracheotome into the trachea and 6-mm tubes were initially inserted in all five cases For reasons described below four of five tubes had to be changed and were replaced by 8-mm tubes.

There were no deaths related to the procedure. Four of the five patients in the Rapitrac group had operative and/or postoperative complications This is statistically significant when compared with three of 20 patients in the Cook group ($P < 0·05$, Fisher's exact test) and two of 16 patients in the conventional tracheostomy group ($P < 0·05$, Fisher's exact test)

Two serious complications occurred in patient no. 4 of the Rapitrac group. Six hours after insertion of the tracheostomy, it occluded causing a rise in airway pressures and bilateral pneumothoraces After the insertion of chest drains, the cause of this problem was found, using a fibreoptic bronchoscope, to be a mucosal flap acting as a one-way valve at the distal end of the tracheostomy tube This mucosal flap was easily removed through the bronchoscope. This tracheostomy had been created using the Rapitrac system and initially the tracheostomy tube had been inserted paratracheally but the problem had been immediately recognized and rectified Misplacement of the tracheostomy tube into the paratracheal tissues also occurred in another one of the five tracheostomies created using the Rapitrac system. This patient also had an air leak from the cuff of the tracheostomy tube just after its insertion. This problem occurred in two other patients on whom the Rapitrac system was used, but was easily remedied by changing the tube. This was done by first inserting a guidewire into the trachea via the tracheostomy tube *in situ* which was then removed leaving the guidewire in place. A new tracheostomy tube was then inserted, mounted on an appropriate size dilator from the Cook system to introduce it over the guidewire. No problems with tube misplacement or damage occurred in any of the tracheostomies made using the Cook system. Tube occlusion, displacement and misplacement occurred in one patient in the conventional tracheostomy group

There was some minor skin edge bleeding in three patients in the Cook group, requiring suture ligation in one case. Bleeding during the procedure was occasionally brisk but was

Table 5 *Comparison of conventional, Cook and Rapitrac tracheostomy*

	Conventional tracheostomy ($n = 16$)	Cook percutaneous tracheostomy ($n = 20$)	Rapitrac percutaneous tracheostomy ($n = 5$)
Median (range) age (years)	55·5 (32–75)	53 (23–79)	64 (33–75)
Median (range) operation time (min)	60 (30–105)	15 (8–70)*	5 (3–15)†‡
Complications			
Operative			
Tube misplacement	1	0	2
Tube cuff air leak	0	0	3
Postoperative			
Wound infection	2	0	0
Tube occlusion	1	0	1
Tube displacement	1	0	0
Pneumothorax	0	0	1
Minor skin edge bleed	0	3	0
Tracheal stenosis	0	0	1

*$P < 0·001$ (conventional *versus* Cook group), †$P < 0·0001$ (conventional *versus* Rapitrac group); ‡$P < 0·05$ (Cook *versus* Rapitrac group, all comparisons, Mann–Whitney U test)

not a problem as it was tamponaded by the insertion of the dilators and the tracheostomy tube. There were no infective complications in any of the tracheostomies created with either of the percutaneous techniques but two wound infections occurred with conventional tracheostomies; these differences are not statistically significant. The cosmetic results after extubation were excellent following percutaneous tracheostomy and there were no cases of tracheal fistula.

One patient in the Rapitrac group developed a minor degree of tracheal stenosis shortly after extubation. Bronchoscopy showed only mucosal oedema and the patient was asymptomatic at review 2 months after discharge from hospital.

Discussion

It has been shown that both types of percutaneous tracheostomy are significantly quicker to perform than conventional tracheostomy, even in patients with adverse operative factors. Of the percutaneous systems, the Rapitrac seems faster, but this must be weighed against the larger number of complications observed. The complication rate with the Cook system compares favourably with reported rates of 25–45 per cent for formal tracheostomy[7,8]. Previous reports of percutaneous tracheostomy[2,9–11] using the Cook type system have also been favourable, with complication rates comparable to those reported here. Previous reports of percutaneous tracheostomy using the Rapitrac system document a much lower complication rate than that presented here. Air leaks from cuff punctures occurred in seven of 80 tracheostomies reported by Schachner *et al.*[4] using the Rapitrac system. There have been no published reports of misplaced tracheostomy tubes.

Both techniques of percutaneous tracheostomy are easy to learn. As with any new procedure there has been a learning curve during which the technique has been refined. Essential to both systems is puncture of the trachea with needle and cannula followed by insertion of the guidewire. The trachea must be adequately fixed to prevent lateral movement during puncture and the endotracheal tube drawn back as far as possible while permitting ventilation Occasionally in elderly patients the trachea may be calcified causing difficulties during puncture Tracheal puncture has not been a problem in patients where neck extension is contraindicated or in patients with a short fat neck. We must, however, caution against use of the tracheotome in patients with a fat neck as the blades of this instrument may be too short to reach into the trachea Although unnecessary in most cases, a fibreoptic flexible bronchoscope can be used to facilitate tracheal puncture. The bronchoscope is inserted via the endotracheal tube already in place. The point of puncture is then transilluminated with the light of the bronchoscope. Correct placement of the guidewire can then be confirmed by direct vision

When using the Cook system we have found that passage of the dilators is eased by making a small (1 cm) incision, either vertical or horizontal, in the skin and subcutaneous tissue. It is not always necessary to use all of the dilators that are supplied with the kit. When inserting the tracheostomy tube it is important to ensure that all air has been aspirated from the cuff. When dilating the track into the trachea with the Rapitrac system it is essential to ensure that the tracheotome is properly seated and fully inserted into the trachea. Considerable difficulty was experienced in inserting an 8-mm tube with the Rapitrac system, the constraints being the space between the jaws of the tracheotome and the fact that the tracheal opening it creates is elliptical. It is during the insertion of the tracheostomy tube through the tracheotome that the inflatable cuff was probably damaged in our patients, despite the cuff being fully deflated. It is for this reason that we abandoned the Rapitrac system. We cannot recommend its use until modifications have been incorporated. One way of modifying the Rapitrac system would be by the addition of a Cook type of dilator, which could be used to push a tracheostomy tube mounted on it through the opening created by the tracheotome, after it has been removed leaving the guidewire in position.

Both types of percutaneous tracheostomy can be easily performed at the bedside. There is therefore minimal disruption to patient treatment and monitoring and the risks associated with moving seriously ill patients from the intensive care unit[12] are removed. Although formal tracheostomy has been performed at the bedside for these reasons[13,14], percutaneous tracheostomy is a simple and more rapid procedure. It is easily performed without a scrubbed assistant and is not dependent on the availability of special lighting or diathermy facilities. Percutaneous tracheostomy appears to offer other benefits, such as the remarkable absence of infective complications and better cosmetic results. This may be due to the reduced disruption of adjacent tissues from the procedure.

It is apparent that percutaneous tracheostomy offers many advantages over conventional tracheostomy. What then, are the disadvantages? In tracheostomies created using the Rapitrac system there was a significantly higher proportion of patients with complications compared with the Cook system and conventional tracheostomy. Until design modification, we would not recommend its use outside evaluation studies. The long-term complications of percutaneous tracheostomy have not been assessed and careful longitudinal studies are needed to identify any problems.

An important issue in the development of this technique is the question of who should perform percutaneous tracheostomy. It is likely that the technique will remain in the domain of surgery, but doctors in the relevant non-surgical specialties such as intensive care and anaesthesia are already skilled in vascular access using the Seldinger technique and could, if they wished, be trained to perform percutaneous tracheostomy. Training should be the responsibility of a surgeon who is experienced in conventional tracheostomy and has gained adequate experience in the percutaneous technique. Surgical backup should always be available if the procedure is performed by non-surgeons.

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Colour Doppler ultrasonography studies of benign and malignant breast lesions

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Colour Doppler scanning was carried out on 53 patients with solid, discrete breast masses. Twenty-five of 32 breast cancers and none of 21 benign lesions gave a positive scan, giving a sensitivity of 78 per cent for association with malignancy, a specificity of 100 per cent and a positive predictive value of 100 per cent. Tumours less than 1 cm in diameter and invasive lobular cancers were least likely to give a positive scan. Axillary node scans were performed in 31 of 32 patients with breast cancer with 29 undergoing an axillary staging procedure. Nine patients had a positive axillary scan and all nine had involved axillary nodes. Three patients had involved axillary nodes, but a negative axillary scan. The sensitivity of colour Doppler scanning for axillary node involvement was 75 per cent, with a specificity of 100 per cent and a positive predictive value of 100 per cent.

As malignant tumours increase in size they stimulate the growth of new blood vesssels by secreting angiogenesis factor[1,2]. These vessels appear to penetrate the lesion from the periphery and often show chaotic anastomoses and shunts[3]. The multiplicity of vessels, their disordered pattern and the presence of arteriovenous shunts give rise to abnormal flow patterns. Carcinomas of the breast, thyroid, liver and kidney show abnormalities of blood flow which can be detected by Doppler assessment[4–10].

Images of breast lesions and axillary nodes can be identified using real-time ultrasonography[11]. Colour Doppler ultrasonography allows mapping of flow signals over the entire area of a real-time ultrasonographic image and allows assessment of flow in and around benign and malignant breast lesions and axillary nodes. Initial studies using colour Doppler ultrasonography to assess breast masses have shown that breast cancers as small as 10 mm are associated with abnormal flow patterns[1]. This study investigates further the value of this technique in the assessment of breast masses, and attempts to simplify the methodology and determine whether colour Doppler ultrasonography can detect axillary node metastases in those patients with breast cancer.

Patients and methods

Fifty-three patients ranging in age from 15 to 71 years underwent colour Doppler examination over a period of 4 months. Patients selected were: (1) a random group of 32 patients with cytologically proven breast cancer; and (2) a random series of 21 patients with a discrete mass which was clinically, cytologically, mammographically (in patients aged over 35 years) and ultrasonographically benign (median clinical size 2·0 (range 0·5–3·5) cm).

All patients underwent fine needle aspiration cytology before colour Doppler scanning, which was performed using a 7·5 MHz hand-held linear ray transducer attached to an Acuson 128 computed sonography unit (Mountain View, California, USA). The Acuson capability for colour Doppler (5 MHz) was used for flow evaluation To make the methods simpler than previously[1], standardized machine settings were used to maximize Doppler sensitivity: the lowest velocity scale (0 06 m/s) and the lowest filter setting to minimize rejection of small frequency shifts. When a solid mass was identified ultrasonographically a colour Doppler image was obtained within the sector of interest. If any clear-cut persistent Doppler signals were seen in or immediately around the tumour mass, this was recorded as a positive scan. The coloration represents flow towards (red) or flow away (blue) from the probe No attempt was made to quantitate the vascularity displayed by colour Doppler scan. A scan using this technique took less than 5 min to perform.

All patients with breast cancer had the clinical size and tumour stage of the lesion recorded, and in those patients who had the lesion excised the pathological size was noted. All patients underwent excision or biopsy of the tumour and have subsequently had their pathology reviewed by a single pathologist (D.P.) who was unaware of the results of the colour Doppler studies. Tumour type, histological grade, the presence or absence of necrosis, inflammatory infiltrate, lymphatic/vascular invasion, sclerosis and the extent of associated non-invasive carcinoma were assessed. The classification of tumour type and assessment of histological features have been previously described[12,13]. Patients with benign lesions have remained under review and all underwent a second ultrasonographic assessment 3 months after the first, which showed either no change or a decrease in size of the lesion.

Patients with breast cancer had the lower axilla scanned. When a node was identified ultrasonographically, colour Doppler ultrasonography was used to assess blood flow in and around the node. Any clear-cut persistent colour Doppler signals in or immediately around the node were recorded as a positive scan. Adequate scans were obtained in 31 patients; incomplete views were obtained in one very anxious patient. Twenty-nine of these patients have had axillary nodes assessed histologically following axillary node sampling (11 patients) or node clearance (18 patients)

Results

Breast cancer

Twenty-five of the 32 patients with breast cancer and none of the 21 patients with benign lesions had a positive scan. The relationship between tumour stage and colour Doppler results is shown in *Table 1*. All three of the negative scans in the T_1 group were in patients with tumours of less than 1 cm in diameter. The four T_2 tumours giving negative scans measured between 2·5 and 4·5 cm. The relationship between tumour histology and scan result is shown in *Table 2*. Only two of five invasive lobular cancers gave a positive scan. Of the two patients with negative scans in the no special type group, one had a

Table 1 *Relationship between tumour stage and results of colour Doppler scan*

Tumour stage	No. of patients	No. of patients with a positive scan
T_1	4	1
T_2	19	15
T_3	5	5
T_{4b}	4	4

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Table 2 *Relationship between tumour histology and results of colour Doppler scan*

Tumour histology	No of patients	No of patients with a positive scan
Microinvasive	2	1
Tubular	1	0
Invasive lobular*	5	2
Invasive carcinomas of no special type	24	22

*Category includes three classical invasive lobular carcinomas and two tubulolobular carcinomas[12]

Table 3 *Relationship between axillary node histology and results of colour Doppler scan of axilla*

Axillary node histology	No of patients	No of patients with a positive axillary scan
Involved	12	9
Not involved	17*	0
Not known	2	0

*Includes the one patient with an equivocal axillary scan

6-mm invasive carcinoma and the other had a 2·5-cm carcinoma with a very sclerotic centre. In total there were five carcinomas which had a marked degree of sclerosis and three of these gave a positive scan. All six patients whose carcinomas had lymphatic/vascular invasion and all five with tumour necrosis had positive scans. No associations were evident between scan results and the other histological features assessed, including overall histological grade, glandular differentiation and nuclear grade.

The sensitivity of colour Doppler ultrasonography for breast cancer was 78 per cent, with a specificity of 100 per cent, a positive predictive value of 100 per cent and a negative predictive value of 75 per cent.

Axillary nodes

Of the 31 axillary scans, 21 were assessed as negative, nine as positive and one as equivocal. In the equivocal scan there were colour Doppler signals a short distance away from a node visible on ultrasonography, and it was uncertain whether this represented normal flow in a branch of the axillary vessels or flow in vessels to the lymph node. The relationship between axillary node involvement and the scan result is shown in *Table 3*. Three patients had involved axillary nodes but a negative axillary scan. Two of these had a primary tumour which was colour Doppler negative and the other patient had a single small nodal metastasis. Of the nine patients with nodal metastases and a positive axillary scan, three had one node involved, three patients had two to four nodes involved, and the other three had axillary metastases in more than four nodes.

The sensitivity of this procedure for axillary node involvement was 75 per cent, with a specificity of 100 per cent, a positive predictive value of 100 per cent and a negative predictive value of 84 per cent.

Discussion

This study shows that colour Doppler ultrasonography has potential in the diagnosis of breast lesions. The advantages of the current method of assessment are that it takes 5 min or less to perform and gives a clear-cut positive or negative result. A positive scan in the current study was seen only in patients with breast cancer, but nearly 25 per cent of breast cancers produced a negative scan. False negative scans were related to tumour size, with tumours below 1 cm in diameter being unlikely to give a positive scan. Invasive lobular carcinomas diffusely infiltrate surrounding breast tissue and in this study were not associated with detectable abnormalities of blood flow in three of five tumours assessed, suggesting that these carcinomas may not be associated with the same focal angiogenesis as carcinomas of no special type.

Initial studies suggested that blood flow could be detected in and around some benign breast lesions, although it was clear that flow was much less than in carcinomas[1]. The simple definition that a scan was positive if any persistent colour Doppler signals were seen, although subjective, makes the assessment of this technique easy in practice All benign lesions in the current series were negative, although fleeting colour Doppler signals have been seen in two more recent patients with fibroadenomas. These signals were not persistent and therefore do fulfil the criteria for a positive scan.

The techniques currently available to assess axillary node involvement are considerably less accurate[14,15]. This study shows that the lower axilla can be assessed using colour Doppler ultrasonography, and all the patients with a positive axillary scan had involved axillary nodes Surgical treatment of the axilla is controversial It has been suggested that patients who are likely to be node-negative are best treated with an axillary node sample whereas those patients who have axillary node involvement are best treated with an axillary node clearance[16–18] This limits the morbidity of axillary clearance to those patients who would benefit from this procedure. Colour Doppler scanning offers one possible method of selecting patients for appropriate axillary surgery, and further studies of this technique are warranted.

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Incidence of arm swelling following axillary clearance for breast cancer

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Arm swelling was measured using volume determination in 118 patients following mastectomy (n = *60*) *or wide excision* (n = *58*)*, both with axillary clearance. The mean age was 60·5 years and the median follow-up was 22·5 months. Axillary clearance removed level III nodes. Axillary irradiation was given to only three patients with extensive* (*more than 75 per cent*) *nodal involvement. The incidence of early postoperative complications was 18·6 per cent. The incidence of lymphoedema was 7·6 per cent* (*nine patients*)*. Three of these patients had early lymphoedema within 6 months of treatment. Arm circumference differences correlated poorly with volume differences. The incidence of lymphoedema following axillary clearance is low and comparable to that for sampling or no axillary surgery.*

Optimal surgery to the axilla in patients with operable breast cancer remains controversial: sampling[1] or full clearance[2]. The main advantages of the latter are the more complete and reliable information obtained regarding nodal status and hence prognosis[3], and reduced recurrence rates while avoiding the possible serious side-effects of axillary irradiation[4].

The incidence of arm lymphoedema has been reported to be greater after clearance than axillary sampling[5,6]. Others, however, have shown a similar incidence of lymphoedema for the two procedures[7,8]. No firm conclusion can be drawn from these studies because the method of assessment of lymphoedema was either subjective[5] or not stated[6]. Where objective measurements have been peformed, the methods have varied and none has been widely accepted.

In this study, arm lymphoedema has been measured objectively in patients with operable breast cancer after an axillary clearance. Axillary clearance was performed for all patients with operable breast cancer undergoing mastectomy or wide local excision Postoperative radiotherapy to the axilla was given to selected patients with more than 75 per cent of lymph nodes involved with tumour

Patients and methods

Patients with operable breast cancer (Union Internacional Contra la Cancrum (UICC) $T_{1-3}N_{0-1}M_0$) and without locoregional recurrence were selected for study. All patients had undergone full axillary clearance in which the axillary fat was cleared from the apex of the axilla, exposing the axillary vein, the long thoracic and thoracodorsal nerves The pectoralis minor muscle was retracted medially to reach nodes medial to its attachment (level III). After wide excision and axillary clearance, breast irradiation of 50 Gy was given over 5 weeks.

Patients answered a simple questionnaire on their subjective assessment of arm swelling after surgery. The volume of each arm was measured by a water displacement technique up to 15 cm above the olecranon This level, marked with the elbow at a right angle, which reflects the volume of the whole arm, has been used by previous authors[7,9,10] The arm was immersed in a tank of warm water up to the predetermined level and the volume of displaced water was measured Arm swelling was expressed as the difference in the volumes of the two arms

The natural asymmetry of the arms due to handedness was compensated for by a correction formula from Godal and Swedborg[11] In their study of 105 healthy Swedish women, a significant difference for right-handed individuals was found of 31 ml For left-handed persons, the difference was less (25 ml) and not significant Similar studies[9,12] have shown the mean differences between arms to be less than 50 ml.

To determine the incidence of clinically significant lymphoedema a working definition of whole arm volume difference of 200 ml or greater[7,13] was chosen With this criterion, possible effects of nodal status, type of surgery and local postoperative complications on arm swelling were assessed using a 2 × 2 χ^2 test.

Volume measurement is more appropriate for assessment of arm swelling[14] but is more troublesome. A simpler measurement which has been used[8,15] is arm circumference To compare the methods, arm circumference was measured at the same level (15 cm above the olecranon) The difference in the upper arm circumference was correlated with the volume difference

Results

A total of 118 patients were studied with a median (range) follow-up of 22·5 (1–126) months The mean (range) age was 60·5 (32–83) years, with 83 per cent of the patients in the postmenopausal age group. Twenty-two (18·6 per cent) patients had UICC clinical stage I (T_1N_0), 34 (28·8 per cent) had stage II ($T_{1-2}N_{0-1}$) tumour and three (2·5 per cent) had stage III (T_3) tumour.

Mastectomy was performed in 60 (50·8 per cent) patients and wide local excision in 58 (49·2 per cent). Full axillary clearance resulted in a mean (range) of 7·9 (3–20) reported nodes. Three patients have had axillary irradiation after mastectomy because of extensive nodal involvement.

The incidence of immediate postoperative complications was 18·6 per cent (seroma 14 patients, wound infection five patients, haematoma three patients), with the majority (82 per cent) occurring in the mastectomy group.

After taking into account the natural asymmetry of the arms (i e right-handed women have a 31-ml greater volume and left-handed women have a 25-ml greater volume), nine patients (7·6 per cent) were found to have lymphoedema using a cut-off value of arm volume difference of 200 ml or more. The mean volume difference in these nine patients was 352·0 ml and no patient had a volume difference of more than 500 ml. Three of these patients have been followed up for less than 6 months.

The incidence of lymphoedema was not affected by the type of breast operation, nodal involvement or postoperative complications (*Table 1*). In five of the nine patients, arm swelling was admitted on direct questioning but no patient was concerned or conscious of it.

The correlation coefficient between arm circumference difference and volume difference was 0·35 with a 95 per cent confidence interval of 0·18–0·49. Arm circumference is not a good measure of lymphoedema when compared with volume measurements.

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Table 1 χ^2 *univariate analysis of the incidence of lymphoedema* versus *patient variables*

	n	Lymphoedema		*P*
		Present	Absent	
Mastectomy	60	5	55	n s.
Wide excision	58	4	54	
Nodes positive	52	5	47	n.s.
Nodes negative	66	4	62	
Postoperative complications				
Yes	22	2	20	n.s.
No	96	7	89	

n.s., Not significant

Discussion

Lymphoedema is an unpleasant complication for the patient (it is ugly and interferes with daily activities) and the surgeon (morbidity measure). It may lead to lymphangiosarcoma, a rare but fatal disease[16].

There is controversy regarding the extent of surgery for the axilla: sampling or clearance[2,17]. Sampling may lead to a lower incidence of lymphoedema.

Since lymphoedema is due to an increase in the amount of interstitial fluid, the most appropriate method of measurement is arm volume[14]. This study shows that arm circumference is not an accurate measure of arm swelling. Only 12 per cent of the variation in the arm volume difference was attributable to arm circumference difference ($r^2 = 0{\cdot}12$). The only study which used volume measurements to assess lymphoedema found no difference in the incidence between sampling plus radiotherapy (9·1 per cent) and axillary clearance (7·4 per cent)[7].

Based on volume measurements and using clinical criteria for lymphoedema the incidence was 7·6 per cent, but three of the nine patients were within 6 months of their treatment and their early lymphoedema might improve[18]. This figure is similar to that in other reports on mastectomy and axillary clearance[16,19,20], wide excision and axillary clearance[5,21,22], and compares well with that for wide excision and irradiation[23]. Arm lymphoedema was only mild or moderate with no patient having severe lymphoedema (volume difference of more than 500 ml).

Routine axillary irradiation after axillary clearance is associated with a high incidence of lymphoedema of 20–30 per cent[5,7,24]. Only patients with extensive nodal involvement (more than 75 per cent) received axillary irradiation; three patients after mastectomy in this study. Others have adopted a selective policy of axillary irradiation when more than 50 per cent of the nodes are involved or when extranodal spread or gross residual disease exists[4]. A rather non-selective policy was pursued in the two studies which reported a lower incidence of lymphoedema after sampling. In one, axillary irradiation was given to 91 per cent of the study population[5], and in the other to all patients with positive nodes[6].

The incidence of lymphoedema based on objective volume measurements in patients treated by axillary clearance and a selective policy of irradiation was 7·6 per cent and comparable to that in patients treated with sampling or no axillary surgery

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Bone mineral content in patients with primary hyperparathyroidism: a comparison of conservative management with surgical treatment

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The management of patients with asymptomatic hyperparathyroidism remains controversial. This study examined the extent to which the presence or prospect of bone disease should influence treatment. Bone mineral content (BMC) of the distal forearm was measured by single photon absorptiometry in 67 patients with mild hyperparathyroidism. Twenty-six patients treated surgically and 17 managed conservatively were reviewed regularly for up to 4 years. Eighty per cent of patients had a baseline fat-corrected BMC within the local reference interval for age and sex, but about 75 per cent of values fell below the mean. BMC at the 'distal' site of the surgically treated patients improved or stabilized, but a continuing decline was seen in the patients managed conservatively ($P < 0{\cdot}01$)*. Differences were small and concern about future osteoporotic fracture should seldom be a major factor in making decisions about surgical correction of mild hyperparathyroidism.*

Automated measurement of serum calcium levels has led to the identification of increasing numbers of patients with asymptomatic primary hyperparathyroidism. The management of this mild disease is controversial[1,2]. Primary hyperparathyroidism may be associated with osteopenia and occasionally with symptomatic fractures. The extent to which the presence or prospect of bone disease should influence treatment is uncertain.

The deficit in bone mineral has been demonstrated in several studies with modern methods of densitometry[2–5]. These reports vary in their assessment of whether cortical or trabecular bone is more severely affected. Many patients, however, have bone densities within an appropriate reference interval[6], and asymptomatic primary hyperparathyroidism does not appear to increase the risk of vertebral fractures[7]. Although parathyroidectomy may lead to a small early increase in bone density, the bone density of surgically treated patients as a group does not reach that of a control population, however long the follow-up[8,9].

Bone mineral content (BMC) has been determined in the forearm in a group of patients with primary hyperparathyroidism and the results compared with those of a local control population. The patients treated surgically were compared with a group of patients who were managed conservatively in follow-up of up to 4 years. The aim was to determine whether a patient's BMC at presentation should influence the choice of treatment given.

Patients and methods

Patients ranged from asymptomatic to those with moderate symptoms The criteria for surgery did not include the bone mineral density measurement or depend on any particular serum calcium level In each patient the serum calcium level returned to the reference range after surgery Conservative management included clinic visits every 6 months to monitor symptoms and serum calcium levels.

Single photon absorptiometry was used to assess the bone status of patients. Using a Molsgaard Medical single photon absorptiometer ND1100A (Nuclear Data, Schaumburg, Illinois, USA) with a ^{125}I source[10], the fat-corrected BMC (BMC_2) of the non-dominant distal forearm was measured in 67 patients (56 women and 11 men) with primary hyperparathyroidism. The 'distal' and 'proximal' regions correspond to the 'ultradistal' and 'distal' regions, respectively, referred to by others[11]

The precision of the BMC measurements was assessed by two operators carrying out the scanning procedure on one female volunteer (age 23 years) on ten occasions. The coefficients of variation (c.v.) were 1·3 per cent for distal BMC_2 (mean 28·5) and 1·2 per cent for proximal BMC_2 (mean 32·2). There were no significant differences between the operators.

The precision of this method compares favourably with that of dual energy X-ray absorptiometry (c.v. 1–1·5 per cent), the current 'gold standard' method for bone densitometry; the precision of dual photon absorptiometry is much lower (c.v. 3–4 per cent). Dual energy X-ray absorptiometry measurements are made at the 'clinically relevant' sites of spine and hip. Single photon absorptiometry measurements, although made at the distal forearm, have been shown to correlate with later fracture incidence[12].

Baseline BMC_2 measurements were expressed as z scores: the number of standard deviations of the patient's value from the age- and sex-adjusted mean of a local reference population The reference interval (2 s.d. either side of the mean) was calculated for each sex from BMC_2 measurements on normal subjects aged between 20 and 80 years (91 men in 10-year age groups and 286 women in 5-year age groups)

Follow-up measurements of BMC for up to 4 years were available on 43 patients 17 without surgery, and 26 after parathyroidectomy. Rates of change of BMC_2 were calculated using the slopes from linear regression on the repeat BMC_2 measurements for individual patients

Eight postmenopausal women who had undergone parathyroidectomy and eight managed conservatively were matched for age as closely as possible and their data pooled to give summary measures, which were then compared using Student's t test. Analysis of univariate correlations was carried out by linear regression with Pearson's correlation coefficients. Student's t test for unpaired data was used to compare the means of BMC_2 (expressed as a percentage of baseline BMC_2 measurement) of patients at 6-month intervals

Results

Eighty per cent of patients had a baseline BMC_2 measurement at both sites within the reference interval for age and sex, and 45 per cent were within 1 s.d. (*Figure 1*). Seventy-three per cent of the values fell below the mean at the distal site and 75 per cent at the proximal site. The mean z score for all patients was $-0{\cdot}85$ (95 per cent confidence interval $-1{\cdot}17$ to $-0{\cdot}53$) for distal BMC_2 and $-0{\cdot}90$ (95 per cent confidence interval

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−1·21 to −0·59) for proximal BMC_2. When expressed as a percentage of the age- and sex-adjusted mean of the reference population, distal and proximal BMC_2 values show reductions of 18 and 16 per cent, respectively.

The age, adjusted calcium and baseline BMC_2 values of the patients for whom follow-up measurements were available are shown in *Table 1*. The BMC at the distal site of the surgically treated patients improved or stabilized, but a continuing decline was seen in the conservatively managed patients (*Figure 2*). The difference between the two groups was not significant at the proximal site (*Figure 2*).

In the two age-matched groups there was no significant difference in mean age or mean adjusted calcium level (*Table 2*). There was a significant difference in the rate of change of distal BMC_2, but this was not seen for proximal BMC_2. Although the baseline BMC_2 measurements at both sites were lower for the parathyroidectomy group than for the conservatively managed group, the difference was not significant.

There was no significant correlation between BMC_2 at either site and adjusted serum calcium levels.

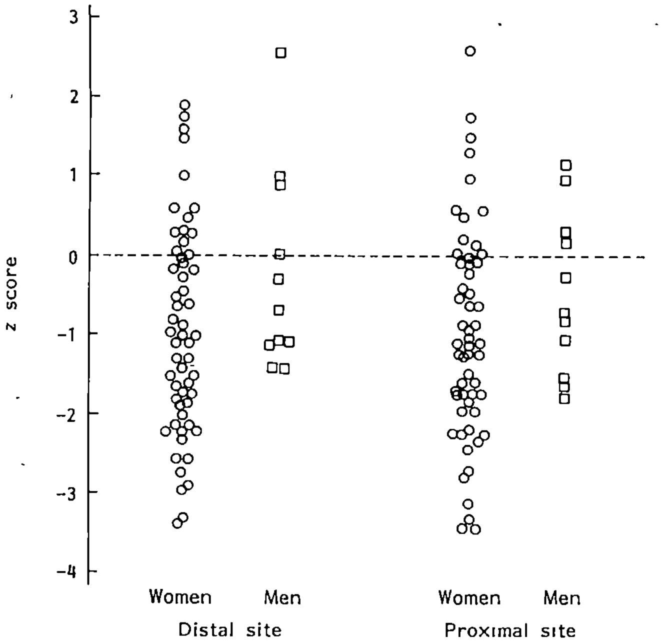

Figure 1 *z scores for bone mineral content (BMC_2) of the non-dominant forearm at two sites in 67 patients with primary hyperparathyroidism The z score is the number of standard deviations of the patient's BMC_2 value from the age- and sex-adjusted mean of a local reference population*

Discussion

This study examined a large population of patients with primary hyperparathyroidism and compared the results with those from a large local control population. Figures for the baseline values in untreated patients with hyperparathyroidism showed that primary hyperparathyroidism induced a modest but significant diminution in BMC. The reduction was similar at the two sites, reflecting losses of both cortical and trabecular bone. These results are in accord with those of Wémeau *et al.*[14], who measured vertebral density in 33 patients using dual photon absorptiometry and found that most had values within 2 s d. of the mean. Other studies have shown a more severe loss; Martin *et al.*[8] found that in the distal and proximal sites about one-third of patients had values more than 2 s.d. below the mean.

BMC_2 reductions compare with mean deficits of 40 per cent for the trabecular bone density in the distal radius and

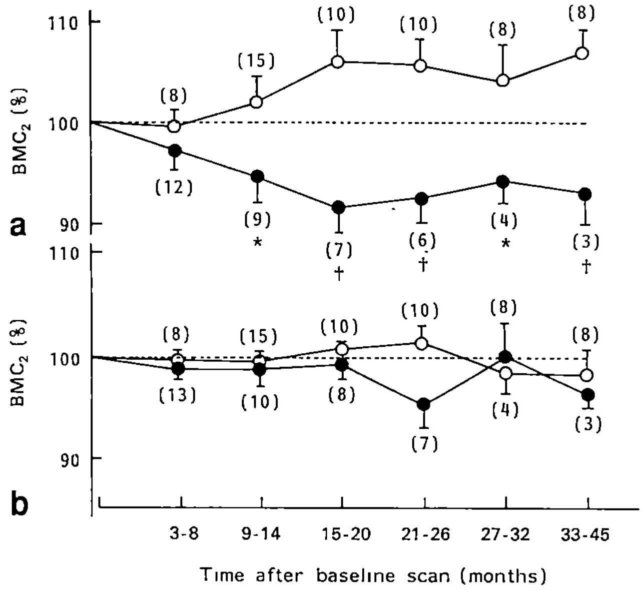

Figure 2 *Fat-corrected bone mineral content (BMC_2) expressed as a percentage of baseline BMC_2 in the non-dominant forearm at* **a** *distal and* **b** *proximal sites in patients with primary hyperparathyroidism, who were managed conservatively* (●) *or who underwent parathyroidectomy* (○). *Values plotted are mean(s.e m.); values in parentheses are the numbers of patients evaluated in each time interval* $^*P < 0·05$, $^\dagger P < 0·01$ (*both parathyroidectomy* versus *conservative management group, Student's* t *test*)

Table 1 *Characteristics at baseline bone mineral content measurement of hyperparathyroid patients in two groups*

	Parathyroidectomy		Conservative management	
	Women ($n = 23$)	Men ($n = 3$)	Women ($n = 14$)	Men ($n = 3$)
Age (years)				
Mean	57	67	67	61
Median (range)	57 (25–75)	64 (62–74)	67 (45–79)	75 (23–84)
Adjusted serum calcium level (mmol/l)				
Mean	2·87	3·26	2·71	2·81
Median (range)	2·76 (2·59–3·83)	3·35 (2·95–3·48)	2·68 (2·55–2·96)	2·75 (2·69–2·98)
Distal BMC_2				
Mean	30·2	50·6	31·4	55·4
Median (range)	27·3 (17·3–52·2)	51·0 (44·6–56·3)	32·6 (8·8–51·9)	59·4 (44·9–62·0)
Proximal BMC_2				
Mean	29·8	45·5	29·6	54·5
Median (range)	27·9 (16·5–46·6)	48·8 (35·2–52·5)	27·4 (11·1–49·9)	51·8 (45·3–66·4)

BMC_2, fat-corrected bone mineral content of the non-dominant forearm Total serum calcium was adjusted for serum albumin using the formula[13]

$$\text{adjusted calcium (mmol/l)} = \text{measured calcium (mmol/l)} + 0·023 \times [40 - \text{serum albumin (g/l)}]$$

Table 2 *Comparisons between eight postmenopausal women who had undergone parathyroidectomy and eight age-matched conservatively managed women*

	Parathyroidectomy	Conservative management	P*
Age (years)	66·8(6·5)	68·0(7·6)	n s
Adjusted calcium level (mmol/l)	2·85(0·29)	2·72(0·06)	n s.
Baseline distal BMC_2	27·0(11·2)	33·0(13·1)	n.s.
Baseline proximal BMC_2	26·7(8·5)	30·8(10·7)	n.s.
Rate of change of distal BMC_2 (per year)			
Absolute units	0·90(0·59)	−1·77(1·53)	<0·001
Percentage of baseline BMC_2	3·24(1·43)	−4·80(5·39)	<0·01
Rate of change of proximal BMC_2 (per year)			
Absolute units	−0·09(0·59)	−0·12(0·77)	n.s
Percentage of baseline BMC_2	0·00(1·68)	−0·25(2·12)	n.s.

Values are mean(s d.) BMC_2, fat-corrected bone mineral content; n s., not significant; *Student's *t* test

16 per cent for cortical bone in the mid-shaft radius measured by computed tomography[3], with 11 per cent in patients examined by single photon absorptiometry of the forearm[9], and with 25 per cent for the forearm and 16 per cent for the vertebrae by computed tomography[4]. In a review by Lafferty and Hubay[2] the percentage reduction ranged between 0 and 32 per cent with a variety of methods.

It is not clear why these figures vary between different studies, there was no relationship between the severity of the loss of density and the severity of the hypercalcaemia[4,8], and there was no relationship between mineral deficit and tumour weight[9].

Follow-up measurements of surgically treated patients have shown a modest improvement at the distal site, reflecting trabecular bone, and no change at the proximal site, predominantly cortical bone, these results are similar to those of Hesp *et al.*[3]. Others have demonstrated an improvement after surgery[8,9,15]. Surgery does not fully correct the deficit, nor does the improvement continue after the first postoperative year, and the bone loss of primary hyperparathyroidism cannot be reversed with surgery[8].

As a group the patients undergoing parathyroidectomy saw a modest improvement in BMC at the distal site, but no further change was seen after about 18 months. The distal BMC decreased in the conservatively managed patients.

The two groups of patients are not comparable and the decision for surgical treatment depended on age, serum calcium levels, symptoms, concurrent illnesses and the patients' own wishes. The age-matched subgroups were not significantly different in serum calcium level; there was still a highly significant difference in the rate of change of BMC_2 at the distal site between these groups

The role of bone density measurements in the choice of treatment in primary hyperparathyroidism remains unclear. Patients have reduced bone mass, but few patients develop symptomatic osteoporotic fractures of the vertebrae[7], perhaps because hyperparathyroidism allows the maintenance of well connected trabecular plates[16]. Surgical correction of hyperparathyroidism does not restore the bone mass to normal, leading to only partial reversal of the deficit in trabecular bone The conclusions of Lafferty and Hubay[2] remain valid, and concern about future osteoporotic fractures should not be a major factor in decision making unless current bone mass is particularly low[17].

Acknowledgements

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Carcinoma in multinodular goitre

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A retrospective review of 107 patients operated on for multinodular goitre was carried out to determine the incidence of carcinoma. Of the group 7·5 per cent harboured incidental carcinomas with papillary carcinoma being the most common variety. The indications for removal of multinodular goitre should be compressive symptoms, suspicion of malignancy and cosmesis.

Multinodular goitre is a benign disorder that affects mainly women. Surgical indications for removal include cosmesis, compressive symptoms, hyperthyroidism or suspicion of malignancy. The incidence of malignancy in multinodular goitres varies from 4 to 17 per cent[1–3] depending on how carefully the surgical specimens are examined. This study examines the incidence of carcinoma in thyroid glands removed for multinodular goitres in a Malaysian population to determine identifying clinical features. The question of whether it is safe to leave multinodular goitres is discussed.

Patients and methods

A retrospective study was carried out of all patients operated on for clinically benign multinodular goitre in this hospital from 1986 to 1990. There were 107 patients who complained of a neck swelling or had compressive symptoms of the trachea or oesophagus. Patients with a single thyroid nodule on clinical examination were excluded. All patients underwent a thyroid hormone assay and most had a technetium radioisotope scan of the thyroid. Patients underwent subtotal thyroidectomy, lobectomy or total thyroidectomy depending on the operative findings. All surgical specimens were sent for histopathological examination.

Results

Of 107 patients 106 were women with a mean age of 35·7 (range 17–74) years.

Eight carcinomas were found (*Table 1*). None of the patients with a carcinoma had a history of neck irradiation. Those with carcinomas were slightly older and had had their goitres for a slightly longer period than those without (*Table 2*).

Table 1 *Pathology of specimens removed*

	No.	Percentage
Benign multinodular goitre	99	92·5
Papillary carcinoma	4	7·5
Follicular carcinoma	2	
Squamous cell carcinoma	1	
Medullary carcinoma	1	
Total	107	100

Table 2 *Patient details*

	Mean age (years)	Duration of goitre (years)
Benign goitres	35·2	5·9
Goitres with carcinoma	45·6	6·8

Discussion

All patients were diagnosed as having a multinodular goitre on clinical grounds. They were offered surgery for cosmesis, symptoms of tracheal or oesophageal compression, or hyperthyroidism. A malignancy was suspected in one patient during operation; the remaining seven malignancies were unexpected findings. Patients with differentiated thyroid carcinomas underwent radioiodine ablation of the remaining thyroid and were put on suppressive thyroxine therapy for life. There were no recurrences on follow-up 1–5 years after surgery. The patient with a squamous cell carcinoma was suspected of having a carcinoma at surgery when a fleshy mass was found in one lobe. She underwent a total thyroidectomy, received postoperative radiotherapy and is well 4 years after surgery with no evidence of locoregional recurrence. The patient with the medullary carcinoma had a sporadic form of the disease with no features of a familial syndrome.

Fine needle aspiration cytology (FNAC) has refined the management of single thyroid nodules[4–6]. Multinodularity poses different problems and 4–17 per cent of resected nodular glands harbour a malignant focus[1–3]. A nodule of cancer may exist which cannot be differentiated by palpation, ultrasonography or radioisotope scanning[6]. It may not be practical to subject a patient with a multinodular goitre to FNAC.

Deaths from metastatic thyroid carcinoma from occult primaries have been documented[7,8] and raise the issue of whether all multinodular goitres should be removed.

Studies by Sokal[9] and Vander *et al.*[10] suggest that the incidence of carcinoma in non-toxic thyroid nodules is low and patients can be followed safely for up to 15 years. If the incidence of carcinoma in all multinodular goitres were of the order of 5–10 per cent, then an increasing mortality rate from thyroid carcinoma should be observed. A degree of selection therefore occurs in those patients operated on and a higher incidence of thyroid carcinoma is not seen in patients from goitrous regions[11].

Several texts state that the carcinoma usually associated with multinodular goitre is of the follicular variety[12,13]. Others agree, however, that it is papillary carcinoma found most commonly[14,15]. The degree of invasiveness of papillary cancers is low and the survival rates of patients with occult and small papillary carcinoma is only slightly lower than for normal persons[14]. Unless a total thyroidectomy is performed in all patients with multinodular goitres, some abnormal thyroid tissue left behind may have malignant potential.

All patients with a multinodular goitre treated conservatively should be closely followed up. Changes in the size of the gland, the appearance of new or hard nodules or lymph nodes may signify malignant change.

Multinodular goitres may harbour an underlying carcinoma, usually papillary in variety. In Malaysia 7·5 per cent of patients with multinodular goitres had a focus of malignancy. There were no reliable features to predict the presence of underlying malignancy.

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Upper thoracic sympathectomy for primary palmar hyperhidrosis: long-term follow-up

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Primary palmar hyperhidrosis is a functionally and socially disabling condition. Upper thoracic sympathectomy is the best curative treatment. Several surgical approaches have been suggested and, recently, less invasive techniques have been communicated. To evaluate which method is the best, the short- and particularly the long-term results must be compared. A series is presented of 170 upper thoracic sympathectomies by the supraclavicular approach performed on 85 patients with palmar hyperhidrosis. Follow-up for a mean of 8·3 years was obtained on 124 operated limbs. The immediate failure rate for relief from hyperhidrosis was 2·4 per cent and hyperhidrosis recurred in another 4·1 per cent of limbs after a period of between 2 and 18 months. Thirteen per cent of patients were dissatisfied with the results of operation, one because of persisting vasomotor rhinitis, two because of Horner's syndrome and five because of persisting or recurrent hyperhidrosis. Satisfactory results in approximately 87 per cent of cases make the operation rewarding. This outcome should be compared with the long-term results of other methods, such as percutaneous phenol injection and the transthoracoscopic approach, when such data are compiled and published.

Primary palmar hyperhidrosis is a pathological condition of excessive perspiration of unknown aetiology. It causes severe emotional, occupational and social handicaps at an early age. An epidemiology study of a young population in Israel[1] showed that 0·6–1·0 per cent complained of excessive sweating of varying degree and anatomical distribution. However, only a quarter of those affected had severe palmar sweating, which represents an incidence of 0·15–0·25 per cent. Palmar hyperhidrosis is best treated by surgical sympathectomy[2–4]. At least eight different approaches have been published[2], each having its merits and drawbacks. Recently, non-surgical sympathectomy has been advocated[5], based on computed tomographically guided percutaneous phenol injections to the upper dorsal sympathetic ganglia. The transthoracoscopic approach, already used in 1942[6] and 1951[7], has also received renewed attention in recent years[8]. To evaluate the best approach for sympathectomy, the short- and long-term results of each technique should be analysed and compared.

This paper describes our experience with the supraclavicular approach to the upper thoracic sympathetic ganglia, reviewing the short- and long-term results of 170 sympathectomies in 85 patients with palmar hyperhidrosis over a period of 15 years.

Patients and methods

Between January 1975 and January 1990, a group of 85 patients underwent upper thoracic sympathectomy for primary palmar hyperhidrosis. Forty-two of the patients were men and 43 were women Their ages ranged from 11 to 45 (mean 22·2) years. All reported that their symptoms had begun 'many years' before their operation, in the majority of cases 'since early childhood'. Twenty-seven (32 per cent) of the 85 patients reported a family history of hyperhidrosis In five (6 per cent) only the hands were affected, 62 (73 per cent) suffered from both palmar and plantar hyperhidrosis, nine (11 per cent) had the axillae affected as well, and the remaining nine (11 per cent) complained of excessive sweating of the whole body

All patients underwent an upper thoracic sympathectomy by the supraclavicular approach[9] Both sides were operated on simultaneously by two teams of surgeons. In all but three patients at least one of two experienced surgeons participated in the procedure Two limbs were reoperated on in the immediate postoperative period. In both cases the sympathetic ganglia had not been resected in the first operation In 157 limbs (92·4 per cent) the lower part of the stellate, the T2 and the T3 ganglia were resected. In the remaining 13 limbs (7 6 per cent) only the T2 and T3 ganglia were removed Frozen section histology on the excised specimens was performed in the majority of cases.

Follow-up was completed on 62 patients (73 per cent) with a total of 124 operated limbs and based on interview answers to a questionnaire. The time lag between the operation and follow-up assessment ranged between 1 and 15 (mean 8 3) years

Results

Immediate results

The immediate results in the 170 operated limbs are presented in *Table 1* From the six limbs in which hyperhidrosis persisted after the operation, two were reoperated on during the same hospitalization with good results. Thus, upon discharge, there were only four limbs in which the phenomenon persisted (2·4 per cent immediate failure rate).

Immediate postoperative complications

The immediate postoperative complications observed during the hospitalization period are listed in *Table 2*. Complications related directly to the operative technique were encountered in 38·8 per cent of operated limbs. Transient Horner's syndrome was usually a temporary event which disappeared before the patient was discharged The persisting cases were those in which signs of the syndrome were still present when the patient left

Table 1 *Immediate outcome correlated with histological results*

	Histology	
	Sympathetic chain	Other
Dry hand	154	2
Humid hand	10	0
Persisting hyperhidrosis	4*	0

*Initially six, but with successful early reoperation in two cases

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hospital. Pneumonia and atelectasis, listed as general complications, were unrelated to pleurotomy, pneumothorax or pleural effusion. In 53 per cent of patients there were no complications whatsoever.

Long-term results

Long-term results are shown in *Table 3*. Patients who reported a 'humid' hand had a slight, almost normal, amount of perspiration on their hand. Of the four limbs in which hyperhidrosis persisted after the operation, one belonged to a patient in whom the other side responded well to the sympathectomy. In this patient histological examination showed sympathetic ganglia on both sides, and cessation of hyperhidrosis in the poorly responding limb occurred a year later. On follow-up, hyperhidrosis was found in five patients, in two on one side only; of these eight limbs, three had hyperhidrosis which persisted from the end of the operation. Thus, hyperhidrosis recurred in only five (4·1 per cent) of 121 limbs. This represents a total long-term failure rate of 8 (6·5 per cent) of 124 limbs. Recurrence of hyperhidrosis developed within 2–18 months after sympathectomy. In all five cases sympathetic ganglionectomy was histologically proven, whereas the operation note suggested that part of the stellate ganglion had been removed in only two of five cases.

Table 2 *Immediate complications after operation*

Complication	*n*
Complications related to the operative technique in 170 operated limbs	
Damage to major lymph vessels	2
Damage to the phrenic nerve	3
Damage to the subclavian artery	3
Pleurotomy	20*
Pneumomediastinum	4
Subcutaneous emphysema	2
Pleural effusion	15†
Local haematoma	3
Wound infection	2
Horner's syndrome	
Transient	4
Persisting	5
Vasomotor rhinitis	3
General complications in 85 patients	
Atelectasis	4
Pneumonia	6
Infusion phlebitis	4

*Persisting pneumothorax drained in one patient, undrained in 13; †chylothorax in one patient

Table 3 *Long-term results in 124 operated limbs*

Results	No. of limbs
Dry hand	96 (77·4)
Humid hand	12 (9·7)
Temporary/partial recurrence	8* (6·5)
Persisting/recurring hyperhidrosis	8† (6·5)

Values in parentheses are percentages *Sweating of the palms occurred occasionally; †three were 'persisting' and five were truly 'recurrent'

Table 4 *Changes in the amount of perspiration from other parts of the body after operation*

Site	No change	Increase	Decrease
Axillae	9	8	8
Trunk	11	33	0
Feet	6	8	9

Late operative sequelae

The late operative sequelae included 13 cases of gustatory sweating. Sixteen patients complained of phantom sweating, which developed in all cases within 18 months of operation. Horner's syndrome related to five operated sides persisted at discharge from hospital; it resolved in two instances within 6 months of operation but in the other three it remained permanently. Of the three cases of vasomotor rhinitis which developed after operation, two had disappeared within 2 weeks and only one persisted. The changes in the amount of perspiration in other parts of the body after operation are listed in *Table 4*.

Subjective evaluation of the results showed that from the 62 patients who were followed up, eight (13 per cent) regretted having been operated on. In five of these patients hyperhidrosis persisted or recurred, two had Horner's syndrome, and one was the patient in whom vasomotor rhinitis persisted. Although some patients complained of increased sweating in other parts of the body as a result of sympathectomy, it was considered by all to be a small price to pay for relief of palmar hyperhidrosis. Fifty-four patients (87 per cent) expressed satisfaction with their operation.

Discussion

A successful case of operative treatment of hyperhidrosis is one in which the sweating is permanently abolished, without any major and persisting complications resulting from the operation. In the majority of series the immediate results are excellent, with more than 95 per cent of hands becoming dry[1,3,10]. A similar result was obtained in the present study In most cases sweating of the hands is completely abolished (in fact an abnormal condition), whereas in a few cases a very mild moisture persists (which actually does not differ materially from the normal condition)[11,12]. There is no rational explanation for this uncommon outcome. It has been claimed that in order to achieve anhidrosis of the hands, the second dorsal sympathetic ganglion should be removed[6,13]. Indeed, in all series, the T2 and T3 ganglia were removed. The necessity to resect the lower part of the stellate ganglion (T1) is still debated, but there is no doubt that an increased incidence of Horner's syndrome is observed when the stellate ganglion is manipulated[14]. The present data include four peculiar failures,

Table 5 *Recurrence of hyperhidrosis in other series*

	Recurrence		Follow-up (years)		Time from operation to recurrence (months)
Reference	*n*	%	Mean	Range	
Cloward[12]	1 of 69 limbs	1	8	1–15	2–18
Bass *et al.*[3]	7 of 133 patients	5	4·5	1–10	4–48
Gjerris and Olesen[18]	1 of 36 patients	3	7·8	2–17	4
Law and Ellis[19]	0 of 18 patients	0	6	1–11	—
Bogokowsky *et al.*[17]	1 of 42 patients	2	—	0·08–5	12
Present series	5 of 124 limbs	4	8·3	1–15	2–18

in which hyperhidrosis persisted despite resection of the T2 and T3 ganglia, proven by histology. On the other hand, two limbs became dry with no histological evidence of ganglial resection. An anatomical anomaly, such as accessory sympathetic ganglia[15], may explain the first occurrence, whereas trauma to the sympathetic chain and section of its branches during the operation could explain the success of the other two cases. Nevertheless, when failure to achieve anhidrosis correlates with absence of ganglia in the histological specimen, an immediate reoperation should be performed. We succeeded in two cases in which these guidelines were followed, as did Adar and colleagues[1]. When in doubt during the primary operation, frozen section histological examination of the resected specimen should indicate failure of excision of the sympathetic ganglia, and thus prevent it.

Most immediate complications after operation are reversible, self-limiting, or have no permanent clinical impact. They may be avoided by meticulous surgical technique. The major complication of this operation is clear-cut Horner's syndrome It differs from the other complications by being irreparable, possibly permanent, and because it causes a severe functional and aesthetic disturbance to the patient. The incidence in the literature varies between zero and approximately 12 per cent; the incidence in this series was 5·3 per cent.

Hartfall and Jochimsen[16] claimed that relapse following a favourable result of sympathectomy for hyperhidrosis is unlikely, thus making long-term follow-up studies unnecessary. This statement is not supported by data in the literature[2,12,17] or by our own results. Both complete late relapse and return of mild moisture have been reported The latter is more frequent and is often considered a favourable end-result, because absolutely dry hands may require the use of moisturizers[11] Recurrent hyperhidrosis on the other hand is a total failure of the procedure and has been observed with a varying incidence (*Table 5*). It appears that, although rare, a recurrence may occur several years after the operation. Resection of the sympathetic ganglia is no guarantee of permanent abolition of hyperhidrosis, as was the case in all the presently described recurrences. A few explanations have been given: regeneration[9,20]; impossibility of producing total sympathectomy of the hands[21]; and sensitization (supersensitivity) produced by the section of postganglionic fibres[22]. Another possible explanation may be anatomical variation and the existence of accessory ganglia and independent sympathetic pathways[15]. Resympathectomy has been advocated[23] and successfully performed, mainly for immediate failure[1,18,24].

It is difficult to explain why in one of the present patients hyperhidrosis ceased only a year after resection of sympathetic ganglia. To implicate late scarring would be completely speculative. Late sequelae include persisting Horner's syndrome, compensatory sweating, phantom hyperhidrosis and gustatory sweating. Only some of the cases of Horner's syndrome persist permanently. However, this is a serious complication and was responsible for the subjective dissatisfaction with the operation in some of our patients and in those of other authors[1]. Resection of the T1 part of the stellate ganglion has been implicated as being responsible for this complication[9,12], but Horner's syndrome has been reported by many authors who resect only the T2–T3 ganglia[1,3,12,25]. We agree with Gelderman[22] that by preserving the upper two-thirds of the stellate ganglion, Horner's syndrome is avoidable. Although we usually resected the T1 part of the stellate ganglion, we had an incidence of only 2·4 per cent of permanent Horner's syndrome, which occurred only in the hands of inexperienced surgeons. Violent manipulation of the sympathetic chain, damaging efferent fibres from the upper part of the stellate ganglion, is probably the cause for this complication in the majority of cases, rather than resection of the T1 portion of the ganglion.

Compensatory sweating is an unexplained increase in perspiration occurring in other parts of the body following upper dorsal sympathectomy. It is the supposed result of a compensatory mechanism[12]. The occurrence of this complication is unpredictable. It has been observed in about one-quarter to two-thirds of cases[3,12,18,19], and reported to start within the first 6 months after operation[18]. In some cases it may subside spontaneously[12]; in others it persists. The opposite effect, namely decrease of sweating in other parts of the body, has also been observed in some of our cases, and has been reported previously[1,12,26]. This makes the explanation of the phenomenon even more difficult. However, it is probably possible to prevent excessive sweating in the axillae. Malone *et al.*[8] always excised the T2–T5 ganglia and always obtained dry axillae. Others[16,27] have claimed that it is sufficient to excise the T4 ganglion to secure dry axillae. Such an extent of resection should be attempted at least in those patients who complain of axillary hyperhidrosis before the operation.

Gustatory sweating, i.e. facial sweating triggered by spicy and some other specific foods, has been reported in between zero and 56 per cent of patients undergoing upper thoracic sympathectomy[25,28]. Observed for the first time by Guttmann[29] in 1931, it has been attributed to sprouting of vagal fibres into the severed sympathetic chain[30,31]. Bloor[32] claimed that resection of the stellate ganglion prevents gustatory sweating. Indeed, Conlon and Keaveny[28], in their series of 135 T1–T3 sympathectomies, did not report this complication. We observed it in 21 per cent of patients followed up, although we had resected the T1 part of the stellate ganglion in the majority.

Phantom sweating, i.e. the subjective feeling of impending hyperhidrosis in the palms without actual sweating, was reported in a high percentage of patients by the group of Mozes and Adar[1,3,26,33]. It is not mentioned in reports of other large series[10,12,20,25,28]. In the present series this complaint was recorded in 26 per cent of patients. It is possible that a direct question put to the patient would have elicited this innocuous sequela of upper thoracic sympathectomy also in other series

The data presented here prove that upper dorsal sympathectomy by the supraclavicular approach is a rewarding therapeutic modality for hyperhidrosis. In expert hands the supraclavicular technique allows a simultaneous bilateral approach, permits access to the T1–T4 ganglia with a relatively low morbidity rate, and arrests hyperhidrosis in almost all cases. Long-term follow-up shows that the final results of sympathectomy for hyperhidrosis differ from the immediate outcome. It also suggests that hyperhidrosis may recur in a small percentage of patients, even years after the operation. In these cases, reoperation may be successful and should be attempted. To supersede the supraclavicular surgical approach, new techniques such as computed tomography-guided phenol sympathetic block and transthoracoscopic sympathectomy should yield at least comparable short- and long-term results. When such data are compiled and published, comparison with the present results will make possible the decision upon the best approach to upper thoracic sympathectomy.

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Recombinant tissue-type plasminogen activator is superior to streptokinase for local intra-arterial thrombolysis

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The results of local intra-arterial thrombolysis in 98 patients treated with streptokinase and 69 patients treated with recombinant tissue plasminogen activator (rtPA) have been compared. The two groups of patients were well matched and their treatment protocols were identical except with regard to the thrombolytic agent used. Strict criteria for defining successful thrombolysis were used. Successful lysis was achieved in 40 of 98 patients (41 per cent) receiving streptokinase and 40 of 69 patients (58 per cent) receiving rtPA ($P < 0\cdot05$)*. The time to lysis was significantly shorter with rtPA, median time 22 h, than with streptokinase, median time 40 h* ($P < 0\cdot002$)*. There was no difference in the incidence of haemorrhagic complications. These results suggest that rtPA is superior to streptokinase for local intra-arterial thrombolysis.*

The treatment of acute arterial thrombosis poses a difficult clinical problem. The disappointing results following balloon thrombectomy or conventional reconstructive surgery[1–3] have led to increasing interest in the technique of intra-arterial thrombolysis. This technique, although practised since the late 1950s, was popularized by Dotter *et al.*[4] in 1974; their regimen of low-dose streptokinase (5000 units/h) remains that most commonly used in the UK today[5].

Despite the popularity of streptokinase for this indication there are a number of potential disadvantages to its use. These relate to its immunogenicity, its aggregatory effect on platelets, its relatively long half-life and its lack of fibrin specificity

Although the reported incidence of anaphylaxis following administration of streptokinase for acute myocardial infarction is low, other allergic reactions are more common[6] and repeated administration of streptokinase is not recommended In addition, in some patients circulating antistreptococcal antibodies may neutralize small doses of streptokinase, rendering lysis less effective Increased platelet activation during thrombolysis, as measured by an increase in urinary thromboxane A_2 metabolites, has been demonstrated in animal and human studies[7,8] and may limit the effectiveness of therapy. There is evidence from *in vitro* studies that part of this increased platelet activation may be a direct effect of streptokinase[9].

Local administration of thrombolytic agents is intended to maximize the concentration at the site of pathology while minimizing the systemic concentration and so minimizing the risk of haemorrhage. To this end the ideal thrombolytic agent is one that is quickly cleared from the systemic circulation Streptokinase, however, has a half-life of approximately 23 min in the circulation[10] and so there is a relative systemic accumulation which may result in an increased incidence of haemorrhagic complications. Finally, as streptokinase causes fibrinogen degradation in addition to fibrin breakdown, the resulting systemic hypofibrinogenaemia is likely to exacerbate any bleeding complications

These disadvantages of streptokinase led to the search for alternative thrombolytic agents, culminating in 1984 with the production by recombinant genetic techniques of tissue plasminogen activator (rtPA)[11]. This agent appears to overcome to a large extent the disadvantages of streptokinase. Being a recombinant human protein it is not immunogenic and so its use is not likely to be associated with either a risk of anaphylaxis or the possibility of neutralization by circulating antibodies. The evidence suggests that it does not cause platelet aggregation[9]. Its half-life is approximately 5 min in the circulation and it is relatively fibrin-specific.

A number of studies have demonstrated that rtPA can be effective in peripheral thrombolysis[12–14], but as yet there is no series comparing rtPA and streptokinase in sufficient numbers to demonstrate significant differences in efficacy. In this study we have reviewed our results for intra-arterial thrombolysis using these two agents over the past 5 years.

Patients and methods

Data have been collected prospectively on a consecutive series of 167 patients presenting between March 1985 and February 1991 and treated by local thrombolysis with either streptokinase (Kabikinase, Kabi Vitrum, Uxbridge, UK or Streptase, Hoechst, Hounslow, UK) or rtPA (Boehringer Ingelheim, Bracknell, UK). Forty patients were randomized between streptokinase and rtPA as part of a larger study, the results of which have been previously reported[15] A further 84 patients were recruited into a series of open studies[16–18] and 43 patients were not included in any trial In total, 98 patients received streptokinase and 69 patients rtPA The dose of streptokinase used was 5000 units/h for all 98 patients. The dose of rtPA was 0·5 mg/h in 51 patients and ranged between 0·25 and 2·5 mg/h in the remainder Despite patients not being randomized between the two agents, the two groups were well matched (*Table 1*)

The technique of thrombolysis has been previously described[16] and has remained the same throughout the study period Briefly, a diagnosis of recent arterial occlusion was made clinically, more than 90 per cent of patients (154 of 167) experiencing a sudden onset of, or sudden marked deterioration in, lower limb ischaemic symptoms within the preceding 30 days. All patients were prepared and consented for thrombolysis before arteriography Arteriography was performed via the contralateral common femoral artery or by intravenous digital subtraction arteriography For iliac, common femoral, or proximal superficial femoral artery occlusions the thrombolysis catheter was sited via the contralateral common femoral artery Occlusions distal to the proximal superficial femoral artery were approached via the ipsilateral common femoral artery In each case the intention was to advance the catheter as far into the arterial occlusion as possible Thrombolysis was performed on the vascular ward and progress monitored clinically and with portable 'single shot' arteriograms at 4 h and then subsequently every 12 h or more frequently as appropriate If, on arteriography, the thrombus distal to the tip of the catheter had been

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Table 1 *Details of patients treated with streptokinase or recombinant tissue plasminogen activator (rtPA)*

	Streptokinase ($n = 98$)	rtPA ($n = 69$)
Median (range) age (years)	68·5 (25–96)	67·5 (42–93)
Sex ratio (M:F)	63·35	54 15
Median (range) duration of history (days)	14 (1–99)	10·5 (1–49)
No. with motor/sensory impairment*	32 (33)	21 (30)
Median (range) ankle·brachial pressure index	0·15 (0·00–0·80)	0·28 (0·00–0·69)
Median (range) length of occlusion (cm)	16 (1–54)	15 (2–70)
Cause of occlusion*		
Embolus	16 (16)	8 (12)
Thrombosis	80 (82)	58 (84)
Graft thrombosis	2 (2)	3 (4)
Site of occlusion*		
Aortoiliac	22 (22)	21 (30)
Femoropopliteal	74 (76)	45 (65)
Graft	2 (2)	3 (4)

*Values in parentheses are percentages

Table 2 *Criteria for successful lysis*

1. Radiological evidence of thrombolysis with recanalization at least as far as the next major collateral
2. Increase in the ankle:brachial pressure index of ≥0·2
3. Limb salvage at 30 days
4. No clinical evidence of rethrombosis (i.e. no reduction in ankle.brachial pressure index)
5. No intervention, other than angioplasty, at the level at which thrombolysis is performed. (Angioplasty, if appropriate, is regarded as an integral part of the procedure Patients having reconstructive surgery remote from the site of lysis may also be regarded as undergoing successful lysis)

lysed, the catheter was withdrawn a few centimetres and lysis continued until either vessel recanalization was achieved or there was no further progress

Patients were regarded as having undergone successful thrombolysis only if there was a significant, sustained, clinical improvement, as defined by the criteria in *Table 2* At review, 30 days after lysis, four categories of outcome were recognized for patients in whom lysis was unsuccessful. These categories were limb salvage following surgery (or further lysis), limb survival without further intervention despite persisting ischaemia, amputation; and death The time to lysis was taken as the time from the onset of the thrombolytic infusion to the time of complete recanalization or maximum radiological lysis. It was recorded in all patients in whom there was radiological evidence of thrombolysis including those in whom there was no clinical improvement Haemorrhagic complications were recorded in three categories: haemorrhagic strokes, major bleeds requiring blood transfusion or surgical intervention, and minor bleeds

Statistical analysis of differences between the treatment groups was performed by χ^2 test or Mann–Whitney *U* test as appropriate.

Results

Initially successful revascularization, defined as radiological evidence of thrombolysis with an increase in the ankle:brachial pressure index of at least 0·2, was seen in 47 of 98 patients (48 per cent) receiving streptokinase and in 49 of 69 patients (71 per cent) receiving rtPA ($\chi^2 = 8{\cdot}8$, 1 d f, $P = 0{\cdot}003$) (*Figure 1*). However, six patients in the streptokinase group suffered rethrombosis within the first 30 days and one patient, despite successful revascularization, still required an amputation because of irreversible necrosis In the rtPA group, seven patients suffered early rethrombosis and a further two died within 30 days from unrelated causes Overall, therefore, 40 of 98 patients (41 per cent) receiving streptokinase and 40 of 69 patients (58 per cent) receiving rtPA achieved successful lysis ($\chi^2 = 4{\cdot}77$, 1 d.f., $P < 0{\cdot}05$). Angioplasty was performed in 18 of the successfully treated 40 patients in the streptokinase group and in 25 of the successfully treated 40 patients in the rtPA group.

The median time to lysis in patients receiving streptokinase was 40 h and in those receiving rtPA it was 22 h ($P < 0{\cdot}002$, Mann–Whitney *U* test) (*Figure 2*).

In 58 patients receiving streptokinase and 29 patients receiving rtPA, thrombolysis failed (*Table 3*). Further intervention was attempted in five of 58 patients receiving streptokinase and in six of 29 patients receiving rtPA. In a further 26 patients receiving streptokinase and 12 receiving

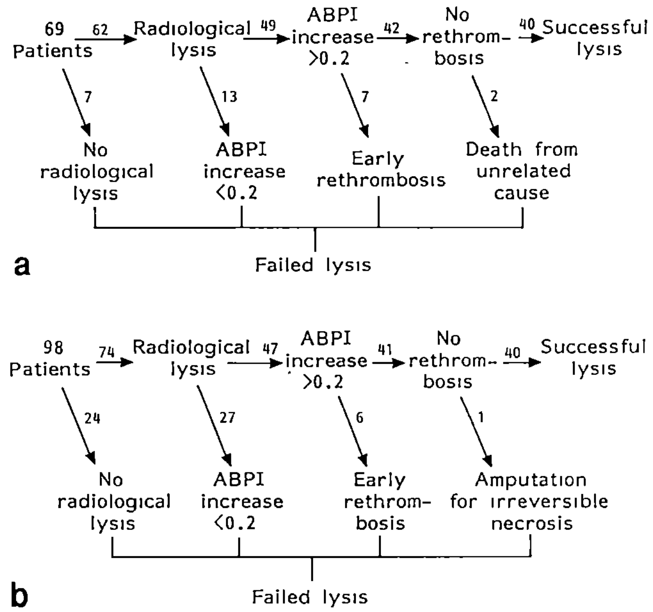

Figure 1 *Flow chart showing requirements for successful lysis and causes of failure in* **a** *69 patients treated with recombinant tissue plasminogen activator and* **b** *98 patients receiving streptokinase ABPI, ankle brachial pressure index*

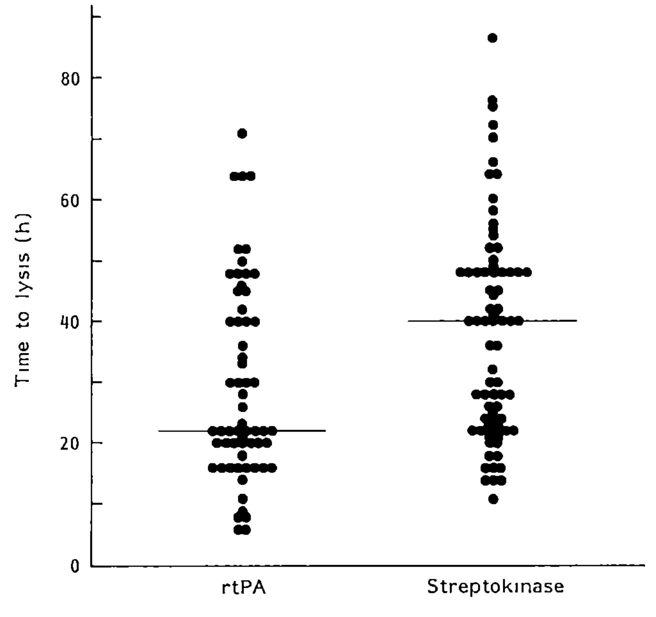

Figure 2 *Scattergram showing times to lysis in patients undergoing thrombolysis with recombinant tissue plasminogen activator (rtPA) or streptokinase Lysis was significantly quicker in patients receiving rtPA (median (bar) 22 h) than in those receiving streptokinase (median (bar) 40 h)* (P < 0 002, *Mann–Whitney* U *test*)

Table 3 *Outcome after thrombolysis for patients treated with streptokinase or recombinant tissue plasminogen activator (rtPA)*

	Streptokinase ($n = 98$)	rtPA ($n = 69$)
Successful lysis	40 (41)	40 (58)
Failed lysis	58 (59)	29 (42)
Limb salvage after further intervention	5 (5)	6 (9)
Limb survival despite persisting ischaemia	26 (27)	12 (17)
Amputation	19 (19)	3 (4)
Death	8 (8)	8 (12)

Values in parentheses are percentages

Table 4 *Complications in patients treated with streptokinase or recombinant tissue plasminogen activator (rtPA)*

Complication	Streptokinase ($n = 98$)	rtPA ($n = 69$)
Haemorrhagic strokes	2 (2)	1 (1)
Major bleeds	6 (6)	4 (6)
Minor bleeds	17 (17)	7 (10)

Values in parentheses are percentages

rtPA, the limb survived despite persisting ischaemia. At 30 days, 19 patients receiving streptokinase were alive after amputation and eight had died; the corresponding figures for rtPA were three and eight, respectively.

The overall incidence of haemorrhagic complications was low and there was no difference in this respect between patients receiving streptokinase and rtPA (*Table 4*). However, of the five patients who suffered either a major bleed or haemorrhagic stroke while receiving rtPA, three had received the highest dose (2·5 mg/h) and there were only two major bleeds in 64 patients receiving the lower doses. The 13 patients who suffered major bleeds or haemorrhagic strokes, when compared with those patients in whom no complications occurred, were found to be of similar age distribution (median age 71 *versus* 68 years, $P = 0{\cdot}28$), similar sex ratio (70 *versus* 69 per cent male) and to have lesions located at similar sites (31 *versus* 26 per cent were iliac artery occlusions). There was a trend showing bleeding to be more common in hypertensive patients (23 *versus* 6 per cent) but this was not statistically significant. The risk of major haemorrhage or haemorrhagic stroke was also observed to be increased in patients who had prolonged infusions. Excluding those who suffered other complications, only 20 patients needed infusions of longer than 48 h, three of these 20 patients suffered bleeding. This is in contrast to only three of 117 at-risk patients who suffered bleeding during the first 12 h of infusion.

Discussion

The rapid development of rtPA for thrombolytic therapy was stimulated primarily by its perceived benefits over streptokinase in coronary thrombolysis. However, despite its theoretical advantages, in the large GISSI-2 study[19] it has been demonstrated to be no better than streptokinase for reducing either mortality rate or severe left ventricular damage in patients presenting with acute myocardial infarction. It is, nevertheless, important not to apply the findings in coronary thrombolysis directly to peripheral thrombolysis without formally testing them, since there are substantial differences between the two therapies with regard to the age and size of the thrombus, and the route, dose and duration of therapy.

For peripheral thrombolysis it is widely agreed that local thrombolysis is superior to systemic thrombolysis, but there has been debate as to which if any of the three currently used thrombolytic agents (streptokinase, rtPA and urokinase) is best. There has been further debate about the most effective dose and method of administration. Current opinion in the UK is balanced between those advocating low-dose continuous infusions, such as described here, and those advocating pulse therapy in which the thrombolytic agent is given as a bolus injection, repeated as necessary. The large multicentre trials required to resolve these debates have yet to be conducted. Furthermore, interpretation of currently available data is difficult due to lack of any consensus on how the results of thrombolysis should be reported. Most publications simply quote the rate of limb salvage at a fixed time point, usually 30 days. It is clear, however, that this figure tends to overestimate the efficacy of the treatment since not every patient in whom lysis fails will require immediate amputation. In some patients the limb can be rescued by reconstructive surgery and in other patients the limb will survive despite persisting ischaemia.

In this study we have drawn up strict criteria to define successful lysis and have used these criteria to report the results in two non-randomized but well matched groups of patients undergoing local thrombolysis using a low-dose continuous infusion regimen of either streptokinase or rtPA. Contrary to the findings in coronary thrombolysis, the results suggest that rtPA is superior to streptokinase in peripheral thrombolysis using this regimen. This advantage of rtPA over streptokinase is manifest both as a substantial increase in the proportion of patients successfully treated and also as a reduction in the time to lysis. This reduction in the time to lysis is probably evidence of greater efficacy. In addition, treatment that succeeds more quickly limits the damage caused by continuing ischaemia, aids patient management and compliance, and reduces hospital stay.

Despite being first performed more than 30 years ago peripheral thrombolysis is still a rarely used technique. It is possible, if the advantages of rtPA over streptokinase found in this study are reflected in practice generally, that more surgeons may be prepared to make wider use of the technique.

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Announcement

Eurosurgery 1992

The 2nd European Congress of Surgery under the auspices of Eurosurgery will take place in Brussels in June 1992. This meeting will pursue the aims of Eurosurgery to promote research and training in surgery.

There will be national sessions sponsored by the Associations of Surgery of all participating nations. Areas of topical interest will be covered in symposia and free paper sessions in areas of general interest and in the specialist fields of abdominal, thoracic, transplantation, trauma, paediatric, endocrine, plastic and vascular surgery. There will be several symposia related to surgical training.

The abstracts of the free paper communications will be published in a special supplement of *The British Journal of Surgery.*

Further details and registration forms may be obtained from the Congress of Secretariat Eurosurgery 1992, Brussels International Trade Fair, Place de Belgique, B1020 Brussels, Belgium. Telephone: 322 477 0457. Facsimile· 322 477 0391.

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Influence of prazosin on experimental vein graft intimal thickening

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The influence of prazosin on experimental vein graft intimal thickening was studied in a rat model. The iliolumbar vein was grafted into the common iliac artery in a prazosin-treated group (n = *17) and a control group* (n = *23). Three weeks after grafting the animals were killed and the grafts harvested. Longitudinal sections were prepared and the intimal thickness measured in the proximal, mid and distal graft. Intimal thickness varied considerably in both groups. Median (range) intimal thicknesses for the control group were: proximal 50 (10–120) μm; mid 30 (10–70) μm; and distal graft 30 (10–100) μm. Results for the prazosin-treated group were: proximal 70 (10–160) μm; mid 25 (5–60) μm; and distal graft 25 (5–135) μm. There was no statistically significant difference in median intimal thicknesses between the control and treated groups.*

Autologous saphenous vein is widely used as an arterial graft and remains the graft of choice for infragenicular and many aortocoronary reconstructions. Unfortunately, up to 30 per cent of these grafts occlude in their first year, and in many cases intimal hyperplasia contributes to this occlusion[1,2] Much is known about the natural history and morphology of vein graft intimal hyperplasia, but the cause, and consequently the treatment, remains uncertain. If vein graft intimal hyperplasia could be reduced, graft patency rates and the results of reconstructive surgery might improve.

Intimal hyperplasia is caused by the proliferation of smooth muscle cells and the deposition of matrix by these cells; it is seen following arterial injury (endarterectomy or angioplasty) and bypass grafting with vein or synthetic material The intimal thickening seen in arteries after balloon de-endothelialization is inhibited by the α_1-adrenergic antagonist prazosin[3] There is also evidence that catecholamines are mitogenic to vascular smooth muscle cells and may exacerbate experimental arteriosclerosis[4,5] The aim of this study was to assess the influence of prazosin on experimental vein graft intimal thickening in a rat model

Materials and methods

Forty inbred male Wistar Firth rats aged 10–15 weeks (weight 340–385 g) were used The rats were housed and cared for in accordance with the Australian code of practice for the care and use of animals for scientific purposes in Australia as proposed by the National Health and Medical Research Council, 1990. Unlimited water and food were provided and the animals were inspected daily The rats were randomized to a prazosin-treated group ($n = 17$) and a control group ($n = 23$) Vein grafts and subsequent morphometric measurements were performed without knowing from which group a rat came

Grafting procedure

All procedures were performed under general anaesthesia using a mixture of oxygen (1·5 l/min), nitrous oxide (0·5 l/min) and 2 per cent halothane with an intraperitoneal injection of pentobarbitone (40 mg/kg body-weight)

The iliolumbar vein graft was performed as previously described[6] A midline abdominal incision was made and the left retroperitoneal region exposed Under an operating microscope the left iliolumbar vein was identified and gently mobilized A 3-mm segment of the vein was resected and placed in a drop of heparinized saline until its use as a graft

Using a mixture of blunt and sharp dissection the left common iliac artery was exposed and mobilized with division of any small branches between the aortic bifurcation and the origin of the internal iliac artery (approximately 1 cm). The proximal and distal artery was clamped in a framed microvascular clamp (Acland 00012V, S and T, Neuhausen, Switzerland) and the vessel divided. The lumen was flushed with heparinized saline and the loose adventitia trimmed The vein graft was interposed between the two ends of the divided artery and the anastomosis performed using interrupted 10/0 monofilament nylon, with approximately ten sutures per anastomosis. The size match between the vein graft and the iliac artery was satisfactory, both vessels being approximately 1 mm in diameter On completion the microvascular clamp was removed and a loose piece of gauze placed over the graft until bleeding from the suture line ceased Once the graft was completed and deemed patent the abdominal wound was closed and the rat allowed to recover from the anaesthetic. Prazosin was administered at a dose of 1 mg/kg twice daily by gavage, starting the day before surgery and continuing until the animals were killed. Control animals received water by gavage

Graft harvesting and preparation

Three weeks after grafting, and 2 h after the last prazosin dose, rats were anaesthetized, the abdominal wound opened and graft patency confirmed by inspection A blood sample was taken from the inferior vena cava for prazosin assay Sera from these samples were stored at −20°C for single batch assay, using the liquid chromatography method described by Reece[7]

Rats were killed by a lethal intrahepatic injection of 20 mg pentobarbitone The thoracic cavity was opened by splitting the sternum and the aorta cannulated via the left ventricle The whole animal was then perfused with 80 ml phosphate-buffered saline followed by 80 ml 10 per cent buffered formalin at a constant pressure of $30\ cmH_2O$ The effluent was drained via the right atrium

Under the operating microscope the grafted left common iliac artery was carefully harvested The specimen was stored in 10 per cent buffered formalin at room temperature until histological processing Specimens were then dehydrated and paraffin blocks prepared The grafted artery was sectioned as a cylinder at six to seven 100-μm levels The four levels closest to the central axis of the graft were selected for morphometry, at each of these levels three slides (three sections per slide) were prepared and stained with haematoxylin and eosin and with an elastin stain (Verhoeff–van Gieson)

Morphometry

Morphometric measurements were made using a microscope fitted with an eyepiece graticule The measurement of interest was the graft intimal thickness This was defined as the perpendicular distance between the inner elastic lamina and the graft lumen The inner elastic lamina could usually be identified as an obvious, discrete condensation of elastin fibres (*Figures 1* and *2*) The intimal thickness was measured in three locations proximal graft 40 μm distal to the proximal anastomosis; mid graft, and distal graft 40 μm proximal to the distal anastomosis. Measurements could not always be made closer to the anastomosis because of lack of definition of the inner elastic lamina For each graft

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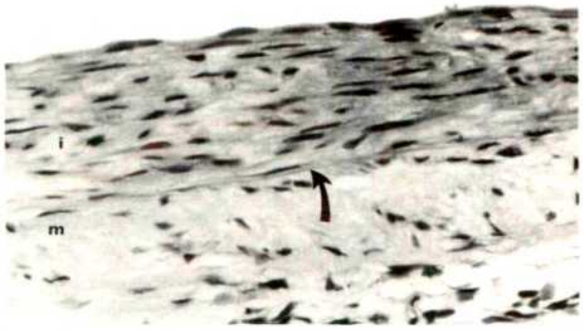

Figure 1 *Marked intimal thickening. Longitudinal section of a vein graft near the proximal anastomosis. The inner elastic lamina (arrow) lies between the thickened intima (i) and the media (m). (Haematoxylin and eosin stain, original magnification × 400)*

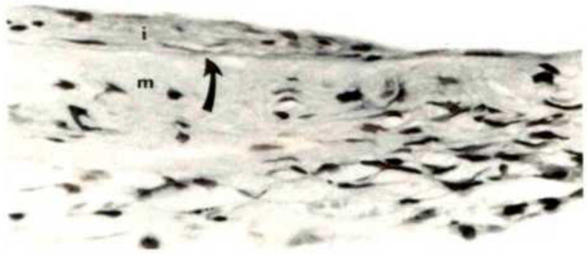

Figure 2 *Minimal intimal thickening. Longitudinal section near the middle of a vein graft. The intima (i) is separated from the media (m) by the inner elastic lamina (arrow). (Haematoxylin and eosin stain, original magnification × 400)*

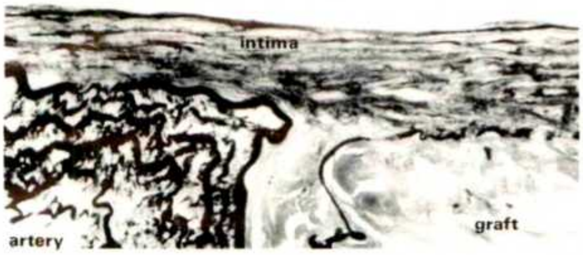

Figure 3 *Longitudinal section of an anastomosis showing the thickened intima either side of the anastomosis. (Verhoeff–van Gieson stain, original magnification × 400)*

the mean of ten to 12 measurements at each of these locations was calculated. The media of the proximal common iliac artery (from the outermost to the innermost elastic lamina) was also measured.

Statistical analysis was performed using the Mann–Whitney *U* test; $P < 0·05$ was taken as statistically significant.

Results

One death of unknown cause occurred in each group. One graft in the prazosin group was occluded; all grafts were patent in the control group. One graft in the control group was damaged during graft harvesting. As a result 21 control and 15 prazosin-treated grafts were available for morphometric assessment. A variable degree of ptosis was noted in all prazosin-treated animals. Prazosin was detected in all serum samples of treated animals, with a mean (range) level of 125 (74–253) mg/l.

The normal iliolumbar vein was only 3–5 μm thick and the intima was barely discernible as a discrete layer. The thickened graft intima consisted of longitudinally arranged spindle-shaped cells in a matrix which stained for elastin, while the graft media consisted of stellate-shaped cells in a collagenous matrix which did not stain for elastin (*Figure 3*). In both groups the intimal thickening was most marked near the anastomosis and tapered off gradually toward the mid-portion of the graft (*Figures 1* and *2*). The proximal graft intima was thicker than that of the distal graft in both the control and the treated groups. Intimal thickening was seen on the arterial side of the anastomosis for variable distances (*Figure 3*). The graft media was thicker than the normal vein wall, but could not be measured precisely as its outer border merged with the loose connective tissue of the adventitia (*Figures 1* and *2*).

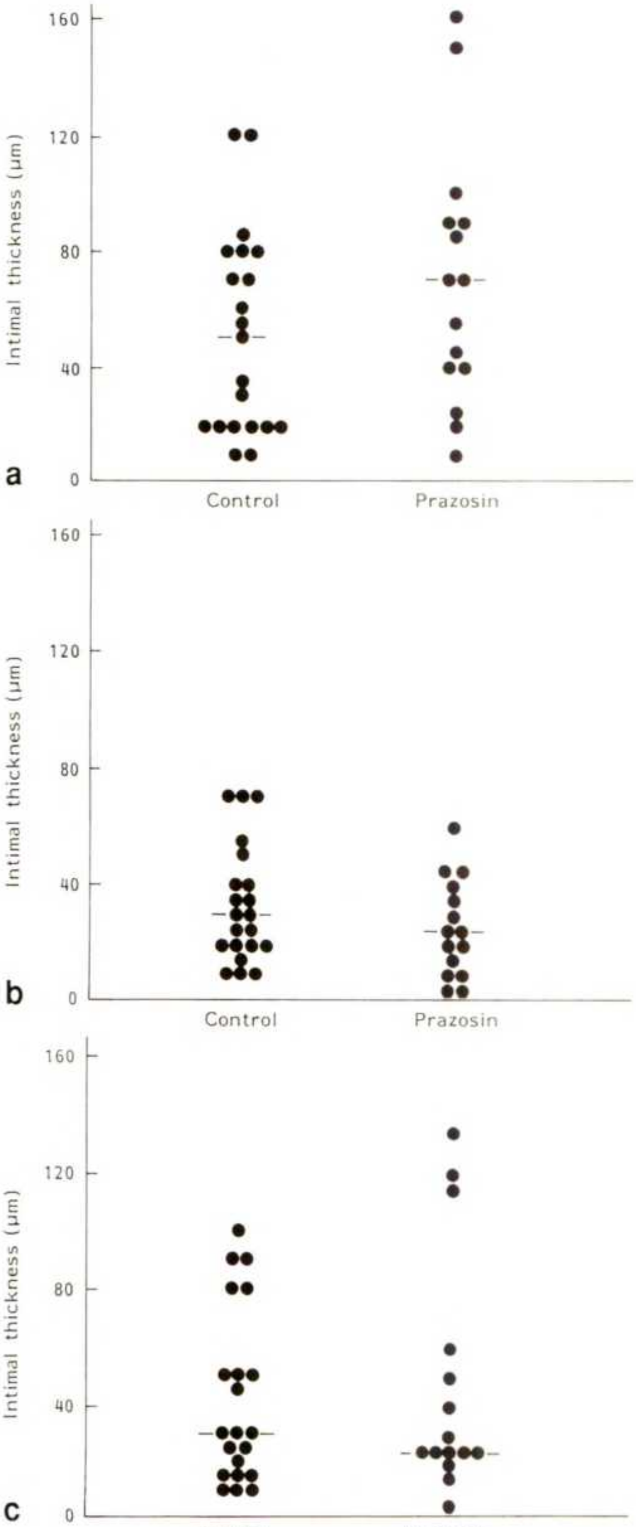

Figure 4 *Distribution of intimal thickness for grafts in the control and prazosin-treated groups. Bars are median values.* **a** *Proximal graft*, P = 0·16; **b** *mid graft*, P = 0·3; **c** *distal graft*, P = 0·76 (*Mann–Whitney U test*)

The distribution of intimal thickness in different parts of the graft was very variable, as shown in *Figure 4*. As the distribution of measurements was skewed, the median and range have been used as statistics. Median (range) intimal thicknesses for the control group were as follows: proximal 50 (10–120) μm; mid 30 (10–70) μm; and distal graft 30 (10–100) μm. Results for the prazosin-treated group were as follows: proximal 70 (10–160) μm; mid 25 (5–60) μm; and distal graft 25 (5–135) μm. There was no statistically significant difference in graft intimal thickness between the control and treated groups at the anastomoses or at the mid graft region (*Figure 4*). There was considerably less variability in the thickness of the proximal iliac artery media: control group 60 (55–70) μm and prazosin-treated group 60 (50–70) μm.

Discussion

Vein graft intimal hyperplasia contributes to the early occlusion of from 15 to 30 per cent of aortocoronary and femoropopliteal grafts[1,2]. Graft intimal hyperplasia has been studied in a variety of animal systems including the rat iliolumbar vein graft model[6,8–10]. Although the histological changes seen in experimental vein grafts are comparable to those seen in clinical specimens, it must be emphasized that the intimal thickening seen in any vein graft model is not identical to the intimal hyperplasia seen in clinical practice. In particular, progressive thickening until graft occlusion occurs is not usually demonstrated in the experimental setting.

Some degree of intimal hyperplasia is seen after any form of vascular intervention including endarterectomy, angioplasty or bypass grafting. Loss of endothelium with subsequent smooth muscle cell proliferation and matrix deposition are key features of the intimal hyperplasia seen after both arterial injury and vascular grafting. The pharmacological control of intimal hyperplasia has recently been reviewed[11]; a number of pharmacological agents, such as heparin, prazosin, eicosapentanoic acid, calcium antagonists and angiotensin-converting enzyme inhibitors, have been found to suppress the intimal hyperplasia seen after arterial injury. It is of interest to examine the influence of these drugs on vein graft intimal hyperplasia. Possible benefit has been detected with heparin[12,13], eicosapentanoic acid[14] and calcium antagonists[15]. Antiplatelet medication has improved early vein graft patency rates in some but not all clinical[16] or experimental[17] studies; aspirin probably reduces graft thrombosis rather than intimal hyperplasia. The effect of prazosin on vein graft intimal hyperplasia has not previously been studied.

Prazosin is a selective α_1-adrenergic blocker used primarily as a vasodilator in arterial hypertension. Prazosin caused a 40 per cent reduction in intimal hyperplasia after balloon de-endothelialization of rat[18] and rabbit[3] aorta. The mechanism by which α_1-blockade inhibits arterial intimal hyperplasia is unclear, although there is recent evidence that interaction with platelet-derived growth factor (PDGF) occurs. Noradrenaline potentiates the mitogenic effect of PDGF on smooth muscle cells by increasing receptor numbers[19]. In an interesting *in vivo* study, a single dose of the α-adrenergic agonist phenylephrine caused a dramatic, though transient, increase in rat aortic PDGF-A gene expression[20]. Although c-*fos* and c-*myc* oncogenes were also induced, the smooth muscle cells did not appear to undergo proliferation and the physiological significance of this observation is unclear[20].

There is evidence to suggest that catecholamines may have a trophic effect on arterial smooth muscle cells. Catecholamines exacerbate experimental arteriosclerosis[5] while β-adrenergic blockade retards arteriosclerosis[21]. Catecholamines are mitogenic to cultured smooth muscle cells, an effect more completely blocked by the α-adrenergic blocker phentolamine than the β-adrenergic blocker propranolol[4]. There is also evidence that sympathetic nerves exert trophic effects on arteries; sympathectomy caused morphological changes and inhibited the increase in DNA mass in the developing rabbit ear artery[22]. Sympathectomy also attenuated vessel wall hypertrophy in the cerebral arteries of stroke-prone rats[23].

Prazosin inhibits the *in vivo* proliferation of arterial smooth muscle cells after balloon de-endothelialization, but has failed to inhibit a similar process in vein grafts. The dose of 1 mg/kg twice daily was chosen on the basis of a previous study[18]. Adequate α-adrenergic blockade appears to have been achieved, as all rats exhibited ptosis during treatment and drug levels at death were high.

The rat iliolumbar vein model has been well characterized in the past[6,8,9]. A survival time of 3 weeks was chosen on the basis of a morphometric study of this model which demonstrated that about 85 per cent of the maximal intimal thickening, especially that near the anastomoses, has occurred by this time[6]. If prazosin had been able to influence intimal thickening in this model, an effect should have been detected by 3 weeks; if the drug influences only the 15 per cent of further thickening seen after the third week, the effect is likely to be small and of doubtful biological significance.

The severity of the intimal thickening in both the control and treated groups was very variable. This problem has been noted in previous experimental studies of vein graft intimal hyperplasia[6,14,17]. Large graft numbers and multiple measurements from each graft were used to minimize the problem. The negative result may be due to a Type 2 statistical error, although the fact that intimal thickening was actually greater at the proximal anastomosis in the treated group makes this unlikely.

There is little doubt that smooth muscle cell proliferation and matrix deposition causes the intimal thickening seen both in injured arteries and in vein grafts. There are, however, differences between the acute injury caused to an artery by a balloon catheter and the chronic haemodynamic and mechanical disturbance occurring in a vein graft. Although loss of endothelium is seen in arterialized vein grafts and appears to be a factor in intimal hyperplasia[8], mechanical factors such as compliance mismatch and abnormal wall stresses, particularly at anastomoses, have also been identified as important factors in graft intimal hyperplasia[10,24]. Prazosin may prevent smooth muscle cell proliferation induced by injury, such as de-endothelialization[3,18], but is unable to overcome haemodynamic stimuli causing vein graft smooth muscle cell proliferation. A similar situation appears to exist with heparin, which inhibits intimal thickening following arterial injury far more than after vein grafting[12,13].

The role of sympathetic reinnervation of vein grafts and its relevance to intimal thickening is unclear[9,25]. Vein harvesting and arterial mobilization result in local sympathetic denervation and there is little evidence that functional sympathetic reinnervation of the rat iliolumbar vein graft has been regained by 3 weeks[9]. Intimal thickening develops despite this local sympathectomy so there is little to suggest that the failure of prazosin to influence graft intimal thickening was due to the absence of trophic effects of sympathetic nerves. A study of the influence of sympathectomy on arterial intimal thickening may clarify this. At present there are insufficient experimental data to support a clinical trial of prazosin for the prevention of vein graft intimal hyperplasia.

Acknowledgements

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Correspondence

Selective uptake of glutamine in the gastrointestinal tract

Sir

In a recent article Mr McAnena and his colleagues report a study on the uptake of the amino acid glutamine by the 'gut' (*Br J Surg* 1991; **78**: 480–2). The authors measured the plasma concentration of amino acids, including glutamine, in the portal vein (close to the liver hilus) and in arterial blood to calculate glutamine extraction. In severe trauma patients, the fractional extraction for glutamine was found to be of the order of 15 per cent.

The large intestine as well as the small intestine also consumes glutamine. Data from a study in four cancer patients in a normal nutritional state showed that peroperative glutamine extraction by the colon is of the order of 10 per cent (*Table*).

Glutamine concentration (μmol/l)				
	Peroperative values			
Normal venous concentration	Arterial concentration	Colonic venous concentration	Venous–arterial concentration difference	Fractional extraction (%)
664(9)	490(60)	446(65)	−44(10)	10(3)

Values are mean(s.e.m.). Fractional extraction ([arterial − venous]/[arterial] × 100) is the percentage of glutamine extracted from arterial blood

When giving enteral nutrition during portal sampling, it is to be expected that the concentrations of, for example, essential amino acids will increase more in the portal vein than in arterial blood. During administration of parenteral nutrition, this will not occur. The observation that the route of nutritional supplementation did not alter the portal arterial differences is remarkable. The fact that the parenterally fed patients included only two subjects stresses the point that this unexpected observation must be interpreted with caution.

A further point of concern is possibly the method employed for blood sampling, sample storage and processing. In a study of 101 postabsorptive venous glutamine concentration determinations in normal persons, using a modern high pressure liquid chromatography technique[2], levels were in the range of 650 μmol/l (*Table*). Although the trauma patients were in a high metabolic stress situation, this value is more than 100 per cent higher than in the authors' report. No control values were presented in the article. Glutamine is an unstable amino acid. Forty-five per cent of glutamine is degraded to ammonia and pyroglutamate[2] at 1 year when the samples are stored at −20°C. Plasma samples for amino acid analysis, including glutamine, must be stored at −70°C as the degradation rate is less than 1 per cent over a 1-year period. The fact that information about sample processing and storage conditions was lacking makes interpretation of the data difficult. We assume amino acid concentrations to be in the range of micromoles per litre?

Portal drained viscera glutamine concentration differences are determined by the glutamine consumption of the small intestine, large intestine and stomach, but also by the pancreas[3] and spleen[4]. The conclusion that selective uptake of glutamine by the *gut* occurs in these patients is therefore, in our opinion, premature. To answer this question, selective venous sampling from the different portal drained viscera is necessary.

We believe that more research is necessary to clarify the role of glutamine in normal and pathological conditions.

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Authors' reply

Sir

Access to the portal circulation using an umbilical vein catheter provided us with the unique opportunity to assess, over a number of days, concentrations of portal *versus* systemic amino acids. This study was performed as part of a study attempting to define factors that could predict the adult respiratory distress syndrome. Institutional review committee consent took 3 years to obtain. Strict criteria were adhered to, and I would submit that a proposal to place an umbilical vein catheter in control subjects undergoing elective surgery for other conditions would be unlikely to be accepted by any institutional review committee. Second, details of the sampling and storage of our assays have just recently been described[1]. Briefly, all these samples were immediately processed and frozen at −70°C. The assays were performed within 8 weeks of sampling. Dr Deutz and colleagues are correct in picking up a typing error. The amino acid concentrations were in the range of micromoles per litre. We agree that selective venous sampling from different portal drained viscera would be ideal. It is noteworthy, however, that previous data from animals have not compartmentalized fractional extraction of glutamine as proposed by the above authors. I think it unlikely that in any scenario it would ever be possible to perform this and certainly not over a 5-day period. While the number of patients was small in our study, the evidence showed that individual concentrations of amino acids measured were no different in either the enterally or parenterally fed group. Our study represents the first human evidence available to us that glutamine is extracted by the gut.

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Rebound tenderness test

Letter 1

Sir

It is unfortunate that the recent paper by Liddington and Thomson (*Br J Surg* 1991, **78**: 795–6) appeared in the same edition as two articles on statistics, as this paper lacks any statistical analysis of the data presented and as a consequence the authors have drawn conclusions from their data which are clearly incorrect.

The sensitivity of 0·81 and specificity of 0·50 found for rebound tenderness suggest that the test has substantial predictive value. These two measures can be combined into a single indicator of the diagnostic value of the test by calculating the odds ratio, which can be expressed as:

$$\frac{\text{sensitivity} \times \text{specificity}}{(100 - \text{sensitivity}) \times (100 - \text{specificity})}$$

Analysing their data, rebound tenderness has an odds ratio of 4·20, with 95 per cent confidence limits of 1·78 and 10·48 and has a highly significant association with the presence of peritonitis, $P < 0.001$.

We have recently published[1] data on 1204 consecutive patients admitted to hospital with right lower quadrant pain, and identified rebound tenderness as an important predictor of acute appendicitis with an odds ratio of 3 36 and $P < 0.001$. Of importance, in a multiple logistic regression rebound tenderness remained significant, indicating that it provides important diagnostic information independent of other symptoms and signs. In their penultimate paragraph, Liddington and Thomson suggest that rebound tenderness might not be relevant once one takes account of other signs such as tenderness and guarding. This is certainly not the case in our study and, in fact, could be tested by the authors on their own data.

We would agree that rebound tenderness as sought by Liddington and Thomson is unpleasant for the patient and for this reason in our study[1] rebound tenderness was assessed principally by percussion of the abdomen, rather than release of the hand after palpation.

In summary, we have demonstrated by analysis of the data of Liddington and Thomson that the presence of rebound tenderness is predictive of peritonitis. Although we would accept that this sign does not have a predictive value approaching 100 per cent, this of course applies to all signs and symptoms associated with peritonitis, which would therefore similarly qualify for the authors' dismissal as 'diagnostically useless'. We have shown that the conclusions drawn by Liddington and Thomson are unjustified and that their data, contrary to their own conclusion, indicate that rebound tenderness is of value in assessment of patients with peritonitis

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1 Dixon JM, Elton RA, Rainey JB, Macleod DAD. Rectal examination in patients with pain in the right lower quadrant of the abdomen *Br Med J* 1990; **302**: 386–8.

Letter 2

Sir

We read with great interest the article by Liddington and Thomson (*Br J Surg* 1991, **78**: 795–6). We are conducting a study which included the assessment of the value of rebound tenderness in the diagnosis of peritonitis The test was found positive in 134 of 145 patients with proven peritonitis This result clearly demonstrates the value of this diagnostic test, in contrast with the authors' findings The way this test is performed does not have to be 'unkind', provided that it is performed properly and accurately.

In this regard we have to stress that test results are as good as the people who perform and interpret them. We continue to demonstrate to our junior staff how to perform and interpret this test correctly.

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Authors' reply

Sir

Although we must confess that Mr Dixon and colleagues' mathematics got past us a bit – even after a preliminary dietary supplement of fish we remained somewhat stumped by the compositional determinants of the odds ratio, let alone their multiple logistic regression – we are grateful for both their and Messrs Hashimi and Stewart's intervention. Looking at our figures again we can readily grasp their point, that even though only 49 per cent of patients who tested positive had peritonitis, the result is significantly better than the similarly derived 37 per cent for plain abdominal tenderness alone

The test in our study had by definition a positive predictive value of only 49 per cent and was therefore of no use as a simple screening measure, but we were wrong to say it had no predictive value, and stand corrected

Whether its residual usefulness justifies its performance in the way generally taught (and employed by us for the study) is another matter Again, Mr Dixon and colleagues may well be right that the percussion test provides the same information but much more kindly

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Bleeding pseudocysts and pseudoaneurysms in chronic pancreatitis

Sir

We read with interest the recent article by El Hamel *et al.* (*Br J Surg* 1991; **78**: 1059–63). Whilst we accept that the mortality rate of untreated cases is 100 per cent[1], we cannot agree that operative treatment is the best first-line therapy for this group of patients. The mortality rate of operation has been reported to be as high as 50 per cent[2], and in the present series it was 33 per cent in those undergoing emergency operations for life-threatening haemorrhage.

An alternative approach is to employ transcatheter embolization of bleeding vessels and pseudoaneurysms. This can be performed in all patients (even those considered unfit for surgery) and avoids the risks of operation. Utilizing such an approach Thakkar *et al.*[3] successfully treated two patients, Baker *et al.*[4] eight patients and Mandel *et al*[5] 15 of 19 patients. There were no deaths attributable to the procedure and no episodes of rebleeding for up to 2 years afterwards. We have recently reported a case of bleeding from a pseudoaneurysm of the pancreaticoduodenal artery successfully treated by transcatheter embolization of the feeding vessels[6] and have since treated a further patient successfully. We have no doubt that transcatheter embolization of feeding vessels represents the best first-line therapy in this group of patients. We also believe that preoperative angiography is essential in all patients requiring operation to control haemorrhage. It provides invaluable information on the site of bleeding as well as identifying the feeding vessels and facilitating the planning of the operative procedures likely to be required.

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Pancreatic tissue and ductal pressures in chronic pancreatitis

Sir

We read with great interest the article on chronic pancreatitis by Jalleh *et al.* (*Br J Surg* 1991, **78**: 1235–7) and agree with the logical policy of excision of the most severely affected part of the gland. However, although in their discussion they suggest that the recordings of 'pancreatic tissue pressure' may reflect parenchymal density rather than intracavity hydrostatic pressure, they do not stress that they are simply measuring the compliance of the tissue and not the hydrostatic pressure. We suggest that the very high readings that they obtained in severely diseased areas of the pancreas merely reflect the degree of fibrosis and calcification, as seen on the computed tomography scan, and not raised pancreatic tissue pressure Surely if the gland has a tissue pressure of 200 mmHg and the duct has a pressure of only 20 mmHg then the duct is hardly likely to be dilated. The concept, therefore, of a 'compartment syndrome' cannot be justified on these data.

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Authors' reply

Sir

We thank Messrs Osborne and Stansby for their comments Unlike hydrostatic pressure in a purely fluid compartment, tissue pressure is a complex physiological concept, and its accurate measurement remains a matter of controversy[1,2] We do not believe that our readings merely reflect tissue compliance, although its contribution is not contested The very slow infusion rate employed served, in part, to clear the intraluminal core of tissue from the needle and could scarcely have caused substantial tissue distension Further, the considerable overlap of pressure recordings in areas with varying degrees of fibrosis and calcification suggests that these features do not entirely account for our measurements. Thus 'pancreatic tissue pressure' reflects a combination of factors

This increased pressure within the confines of the pancreas is, by definition, a 'compartment syndrome'[2]. Recently, another group has used the term in an even broader sense, describing inability of an experimentally induced pancreatitis model to distend and dissipate pressures generated by pancreatic secretion[3] The idea that pancreatic ductal ectasia develops as a consequence of increased pressure may be too simplistic We have been struck by the relatively low ductal pressures in these patients and by the absence of tight stenoses It may be that the duct dilates to occupy space released by parenchymal scarring and contraction.

Whatever the theoretical arguments, our technique has enabled quantification in a difficult area. In a more practical sense, its clinical use may aid the understanding and operative management of chronic pancreatitis

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Colonic perforation during colonoscopy

Sir

We read with interest the paper from Miss Hall and colleagues on the subject of colonic perforation during colonoscopy (*Br J Surg* 1991, **78** 542–4) Having identified 17 patients who had perforation of the colon during colonoscopy they conclude by recommending a form of treatment which was used on only one patient in their study Colonic perforations from any cause can be treated conservatively at first if the patient has a localized perforation with no signs of generalized peritonitis. The authors have also commented that the mortality rate for surgical treatment of this condition is greater than that for conservative treatment They make no comment, however, that it is those patients who have localized perforations who are more likely to be treated conservatively and those patients with generalized peritonitis who are more likely to be treated surgically and also have a higher mortality rate from their peritonitis They have also commented on two papers by Adair and Hishon and by Andresen on perforation of the colon and rectum after sigmoidoscopy and proctoscopy. Adair and Hishon treated four patients conservatively but three of these were rectal perforations, two of which had only retroperitoneal gas present on radiography Andresen treated nine of 94 cases of sigmoidoscopic perforation without surgery and it is quite possible that some of these nine cases were also extraperitoneal perforations

Miss Hall and colleagues are in great danger of encouraging surgeons and physicians to delay surgery in cases of colonoscopic perforation. They unfortunately omit to say that conservative therapy should be considered only when signs of generalized peritonitis are absent and the patient's general condition is good, advice which is given in the 1981 paper by Adair and Hishon.

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Authors' reply

Sir

We are pleased to see that our paper has received continued interest. Messrs Charnley *et al.* indicate that patients with generalized peritonitis (and therefore very ill) are more likely to need operation and have a higher mortality rate than those treated conservatively due to a 'localized' perforation (and therefore less ill) This we would obviously all agree upon. But that is not the only factor – the operative stress, especially if there is coexistent respiratory or cardiovascular disease, *will* contribute to mortality.

Restriction of space prevented us from giving details of the one patient who was treated conservatively Within 2 h of colonic polypectomy this 48-year-old man had a temperature of 38 5°C, pulse 120/min, blood pressure 100/60 mmHg, a large amount of gas under the diaphragm on an erect chest radiograph and signs of peritonitis in the lower half of the abdomen. Early institution of conservative measures (nasogastric tube, intravenous fluids and antibiotics, nil by mouth and close monitoring) enabled the patient to be discharged at 5 days Was this 'localized' or 'generalized' peritonitis and just how 'good' would they describe the patient's initial condition? Moreover, there were three other patients with free gas in the peritoneum at laparotomy but in whom the site of perforation could not be identified, and they were given a 'blind' defunctioning colostomy and external drainage Were all these operations justified? We are therefore not simply referring to cases of retroperitoneal perforation

In many cases the decision to operate or treat conservatively is a difficult one, thus the problem should not be oversimplified We wish to stress the points we made in our paper: (1) more frequent consideration should be given to a *trial* of conservative management, (2) this should, however, not allow an irretrievable surgical situation to develop; and (3) the endoscopist *must* therefore discuss the problem with the surgeon at an early stage

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Endothelium-derived relaxing factor and vein grafts

Sir

We read with interest the review article by Komori *et al.* (*Br J Surg* 1991; **78**: 1027–30). They emphasize the important role of the endothelium in modulating the underlying vascular smooth muscle by releasing endothelium-derived relaxing factor (EDRF), which is a potent vasodilator and inhibitor of platelet aggregation. In addition, they speculate on the possible relationship between decreased EDRF production by a functionally injured endothelium and the development of both vasospasm and intrinsic graft lesions.

However, their article concentrates on reversed vein grafts where the effects of surgical preparation of the graft on EDRF production are well established[1], but they make no mention of the *in situ* technique. In femorodistal bypasses to below the knee this technique is the method of choice because it has the advantage of a better size-match between artery and vein graft at each anastomosis. Despite the fact that the vein is often fully mobilized[2] and a valvulotome is passed along its lumen to destroy the valves, it has been suggested that this technique leads to superior endothelial preservation when compared with the reversed method[3].

We have recently investigated endothelial and smooth muscle cell injury during preparation of both reversed and *in situ* vein grafts[4]. Whilst we agree that EDRF production is reduced after preparation of reversed vein grafts, it is absent after preparation of *in situ* grafts because of severe loss of endothelial cells and functional impairment of any remaining cells. In addition, preparation of reversed and *in situ* vein grafts also leads to injury to the smooth cells of the media.

It is likely that cellular injury plays a role in the subsequent development of intrinsic lesions in infrainguinal vein grafts which are an important cause of failure in the first postoperative year. Recently a link has been established between endothelial and smooth muscle cell injury during preparation of reversed vein grafts and intimal hyperplasia in an organ culture system[5]. Therefore the importance of endothelial loss and absent EDRF production associated with the *in situ* technique warrants further study.

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Blood transfusion and recurrent Crohn's disease

Sir

Mr Phillips and colleagues discuss blood transfusion and recurrent Crohn's disease in a recent number of the Journal (*Br J Surg* 1991, **78**: 455–8). They found that blood transfusion did not affect the cumulative recurrence risk. However, they did not state the indications for transfusion. *Table 1* in the paper shows that the transfused patients had a mean(s.d.) haemoglobin value of 11·7(1·3) g/dl. Nineteen patients received 1 unit and 49 received 2 units of blood.

As the patients were young (mean(s.d.) age of transfused group 31·2(11·2) years) and were operated on for primary Crohn's disease, it is important to ask whether it was really necessary to transfuse them with a single unit of blood. We try to avoid giving single units on account of the tentative risks of transfusion. We believe that a patient can stand a low haemoglobin value of 7·0–8·0 g/dl without any risk of complication, especially a young patient who can produce his or her own red blood cells easily if supplemented with iron.

Should we not be more restrictive with blood transfusion and ask our anaesthetists to reserve it for those who really need it?

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Authors' reply

Sir

I entirely agree with the sentiment expressed by Messrs Modin and Wählby. There is no place for single unit blood transfusion, and many patients can be left, as they suggest, with a low haemoglobin which will recover with haematinics. For many reasons blood transfusion should be avoided; indeed, it is because of this that I now perform all dissection with the diathermy set on a coagulating current and this gives a remarkably dry field

The reported study looks back in time as much as 44 years when ideas were different; indeed, just 10 years ago a haemoglobin less than 10 g/dl was an absolute indication for blood transfusion. How times have changed!

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Notices and announcements

24 March 1992
Study Day on Management of Pancreatic Cancer
Southampton, UK
Information Mrs J Daniels, University Surgical Unit, F Level Centre Block, Southampton General Hospital, Tremona Road, Southampton SO9 4XY, UK

30 March–4 April 1992
Head and Neck Oncology: Current Issues and Recent Advances
London, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

1–3 April 1992
Association of Surgeons of Great Britain and Ireland Annual Meeting
Jersey, UK
Information Ms Caroline Ross, The Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

13–14 April 1992
Injury Research Group 1992 Meeting
Manchester, UK
Information Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

13–15 April 1992
1st Portuguese–Spanish International Meeting on Colorectal Pathology
Lisbon, Portugal
Information· Dr Antônio Castro Mendes de Almeida, University Hospital of Santa Maria, Medicina Operatória, Piso 2, 1699 Lisbon Codex, Portugal

22–25 April 1992
Updating Course on Pancreatic Diseases
Genoa, Italy
Information. Organizing Secretariat, QB Service, Via Visconti Venosta 4, 21122 Milano, Italy

22–25 April 1992
2nd International Workshop and Symposium on Therapeutic Endoscopy and Gastroenterology
Shanghai, China
Information Dr J W C. Leung, Department of Medicine, Prince of Wales Hospital, Hong Kong

3 May 1992
8th Special Regional Symposium on the Modern Treatment of Varicose Veins
Baltimore, Maryland, USA
Information· North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, CA 92024, USA

3–7 May 1992
7th International Congress on Senology (Breast Diseases) of the Senological International Society
Rhodes, Greece
Information Congress Secretariat, 102 Michalakopoulou Street, GR-115 28 Athens, Greece

5 May 1992
Surgery in the Developing World – The Challenge to Britain
London, UK
Information Keith Newton, Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, UK

10–16 May 1992
Acute Trauma Management
Belfast, UK
Information· Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

15 May 1992
Abdominal Aortic Aneurysms – Assessment and Management
Ayr, UK
Information Mr G. Stewart, The Ayr Hospital, Dallmington Road, Ayr KA6 6DX, UK

17–23 May 1992
Recent Advances in Endocrinology and Metabolism
Edinburgh, UK
Information Courses Department. The British Council, 10 Spring Gardens, London SW1A 2BN, UK

20–23 May 1992
83rd Meeting of the American Association for Cancer Research
San Diego, California, USA
Information American Association for Cancer Research, Inc, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, PA 19106-3483, USA

27–29 May 1992
European Council for Coloproctology Fourth Biennial Congress
Marseille, France
Information Patricia Vallet, Alice Congrés, 12 Cours Jean Ballard, BP 2028 13201 Marseille cedex 01, France

2–5 June 1992
Eurochirurgie '92 2nd European Congress of Surgery
Brussels, Belgium
Information Congress Secretariat: Eurosurgery '92, Brussels International Trade Fair, Place de Belgique, B-1020 Brussels, Belgium

7–10 June 1992
International Congress on Cancer of the Esophagus
Genoa, Italy
Information Secretariat, Luigina Bonelli, Unit of Clinical Epidemiology and Trials, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

7–11 June 1992
4th World Congress of Hepato-Pancreato-Biliary Surgery
Hong Kong
Information. Secretariat, International Conference Consultants Ltd, Suits A and B, 16/F., Casey Building, 38 Lok Ku Rd, Sheung Wan, Hong Kong

9–10 June 1992
Specialist Short Course: New Trends in Pathology
London, UK
Information J Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

15–19 June 1992
Specialist Short Course: Advances in Haematology
London, UK
Information J Ashton, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

24–27 June 1992
The Endocrine Society 74th Annual Meeting
San Antonio, Texas, USA
Information Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

28 June–3 July 1992
4th Oxbridge Organ Transplantation Course
Cambridge, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

29 June–3 July 1992
Practical Nutritional Support – Third Annual Training Course for Clinicians
Southampton, UK
Information Mr Brendan Moran, Department of Human Nutrition, University of Southampton, Southampton SO9 3TU, UK

2–3 July 1992
Surgical Research Society Meeting
Edinburgh, UK
Information Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

5–10 July 1992
Immunology and the Nervous System: Clinical Aspects
Oxford, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

10–11 July 1992
Hong Kong Surgical Forum – Summer 1992
Hong Kong
Information Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

10–12 July 1992
Minimally Invasive Medicine – From Diagnosis to Therapy
Berlin, Germany
Information KIT Marketing Services GmbH, Behrenstraße 23, 0-1080 Berlin-Mitte, Germany

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The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full Permission to use published work must be obtained from the original author and the publisher before submission

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg) Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984, **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title, place of publication, publisher; year of publication, page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications* New York: Springer-Verlag, 1981: 123–63

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991, **78**: 782–4 The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished The use of the '±' symbol should be avoided, these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values

Interpretation

Statistical significance should not be confused with clinical significance In particular, 'negative' findings should be interpreted through the use of confidence intervals

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data

Leading article

Br. J. Surg. 1992, Vol. 79, April, 289–290

Laparoscopic appendicectomy

Interest and enthusiasm shown by general surgeons for therapeutic laparoscopy is rapidly becoming a global phenomenon. The speed of adoption and popularity of laparoscopic cholecystectomy is without precedent in modern surgical history, despite the relative lack of information concerning its morbidity, cost-effectiveness and long-term consequences[1–3], and the fact that some surgeons advocate a more cautious approach[4]. Although laparoscopic appendicectomy was reported 4 years before laparoscopic cholecystectomy[5], it has not had such a meteoric rise and is practised routinely in only a few centres[6–9].

Why should one bother to remove the appendix laparoscopically when most surgeons claim that they can perform appendicectomy through a small cosmetic incision with minimal complications and a short hospital stay[10]? Unfortunately the facts are somewhat different. Not infrequently, difficulties are encountered which require enlargement of the incision, and even then the ability to evaluate the entire abdomen in a patient found to have a normal appendix is limited. Wound infection rates of 4–7 per cent are still reported following appendicectomy despite the use of prophylactic antibiotics[11]. Furthermore, in a review of over 10000 patients, postoperative pelvic abscesses were shown to complicate the procedure in 3·5 per cent of cases[12]. Other problems relate to the formation of adhesions which may be a source of persistent pain or late bowel obstruction, infertility in women, and to the incidence of incisional hernia and the increased chance of developing a right inguinal hernia. A recent survey of over 2000 patients undergoing emergency appendicectomy in the south-west Thames region showed that the average hospital stay was 4·6 days.

Evidence that laparoscopic surgery provides a better approach is still very limited, but four large series have now reported it to be a safe procedure[6–9]. Early experience suggests that patients have improved cosmesis, a decrease in morbidity, a reduction in wound pain, a shortened hospital stay, and a quicker return to normal life. There is also some evidence that the development of adhesions may be reduced[13]. These findings accord entirely with our own experience of more than 30 cases. Laparoscopy allows both an excellent exposure of the appendix, regardless of its position, and a thorough examination of the rest of the abdomen. It is already an established tool as an aid to diagnosis in young women with abdominal pain and may shorten delay in treatment. Wound infection should be significantly decreased if the appendix is inserted into a bag before its removal; the theoretical risk of increased intra-abdominal abscess formation related to abdominal insufflation has not been substantiated[6–9]. Another consideration is the possible decreased risk of transmission of human immunodeficiency (and other) viruses due to the reduced contact with blood. Evisceration, herniation and small bowel obstruction can largely be avoided by checking all cannula sites before removal of the laparoscope and taking care in closing the rectus sheath.

Two of the major criticisms of laparoscopic appendicectomy are that it takes longer to perform than the open procedure and that there is a need to purchase and maintain sophisticated electronic instrumentation. We agree that in the learning phase the former is true, although with experience laparoscopic appendicectomy need take only 15–20 min[8,9]. We also agree with Holohan[1] that there will always be surgeons operating without adequate laparoscopic training and, more importantly, without the judgement to appreciate this lack of knowledge. This is a sad fact of life but it should not be allowed to hinder the development of new 'patient-friendly' techniques. We believe it is essential that an experienced and skilled laparoscopist should directly assist junior surgical staff until they are competent to operate on their own. In this context it is ironic that most surgeons start therapeutic laparoscopy by learning laparoscopic cholecystectomy although appendicectomy is both easier and safer. The latter procedure should allow our future generation of surgeons to be properly trained in laparoscopic techniques. The problem of equipment will soon be irrelevant as the instrumentation will become generally available in line with the increasing range of procedures performed. The development of new technology may make laparoscopic appendicectomy quicker and safer. Already there are instruments

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available which may be used to staple across the caecum should the appendix be perforated or necrotic at its base.

No prospective randomized trial carried out by surgeons of comparable experience comparing laparoscopic with open appendicectomy has yet been reported. Even so, laparoscopic appendicectomy has potential benefits for patients; it is also possible that earlier discharge from hospital and a rapid return to full activity may show the laparoscopic operation to be a more economical exercise. These and other aspects are being investigated in such a trial now underway at this hospital.

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Digest

Der Chirurg

Zeitschrift für alle Gebiete der operativen Medizin

Organ des Berufsverbandes der Deutschen Chirurgen e V
Organ der Deutschen Gesellschaft für Chirurgie

Br. J. Surg. 1992, Vol. 79, April, 291–292

Readers will be aware that in last month's issue of the Journal we carried a digest of recent papers from The American Journal of Surgery. *This month we are repeating the experiment with the German journal* Der Chirurg. *Professor Christian Herfarth, Editor of* Der Chirurg, *has identified four papers of particular interest that appeared in that journal towards the end of 1991. A reciprocal digest of papers from* The British Journal of Surgery *is being carried in* Der Chirurg. *We hope that readers will enjoy this interchange of material with our sister journals in Europe and North America Any contentious points for the Correspondence column should be addressed to the primary journal, though we would be glad to receive a copy.*

Treatment strategy for primary inoperable carcinoma of the rectum

J. Th. Plukker, L. M. Buhre, R. K. J. Simmermacher, R. C. J. Verschueren, D. M. Mehta, J. A. Schreiner and J. Oldhoff

Chirurg 1991; **62**: 720–4

Patients with locally advanced rectal tumours receive preoperative radiotherapy (50–54 Gy over 5–6 weeks) to reduce the tumour bulk and allow radical local treatment.

Despite extensive preoperative work using computed tomography, nuclear magnetic resonance imaging or endosonography, the local operability of rectal tumours cannot be determined with sufficient accuracy to allow precise preoperative local staging. The authors therefore routinely perform a bimanual examination of the pelvis and rectum after laparotomy to determine whether local tumour control can be achieved and a potentially curative operation performed. If bimanual examination reveals that complete local excision of the tumour is not feasible, an end colostomy of the descending colon is performed The distal colon is brought out as a mucous fistula through the lower end of the laparotomy incision (modified Hartmann's operation) to exclude the distal large bowel from the faecal stream and prevent dilatation and subsequent perforation, thus facilitating radiotherapy. The second operation aimed at being curative is performed 4 weeks after the completion of radiotherapy.

The authors report on experience of 123 patients treated with this protocol over a 9-year period to January 1989. Nine patients had local therapy and 16 preoperative radiotherapy for locally advanced disease Twenty-two of the remaining 98 patients were found on intraoperative bimanual examination to be inoperable and an end colostomy of the descending colon with blind closure of the distal colon was performed (here the manuscript is inconsistent). Tumour removal was possible at second laparotomy in all but four patients with locally advanced disease. In 13 of these 18 patients a curative operation was performed. Complications included one patient with bleeding from the sacral venous plexus and one patient with ileus; both required reoperation. Histological evaluation of surgical specimens revealed no tumour ($n = 1$), Dukes' A ($n = 1$), Dukes' B ($n = 7$) and Dukes' C ($n = 4$) lesions, indicating that radiotherapy was effective in reducing tumour infiltration. On follow-up only two of 18 patients had evidence of local recurrence, and seven of the 13 who had undergone curative operations had no evidence of recurrence after a mean follow-up of 41 months.

The authors conclude that intraoperative bimanual examination of the pelvis improves clinical staging and that defunctioning of the distal colon and rectum facilitates intensive radiotherapy This protocol may be useful for the management of patients with locally advanced rectal carcinoma.

Ultrasonography in suspected acute appendicitis. Option or obligation?

A. Ziehlke, U. Malewski, R. Lindlar, R. Förster, H. J. Klotter, J. Rüschoff, H. Sitter and M. Rothmund

Chirurg 1991; **62**: 743–9

This study was designed to determine the value of ultrasonography in the diagnosis and treatment of appendicitis when used by four surgeons with only average experience. Patients admitted with a diagnosis of suspected acute appendicitis were categorized on clinical examination as: (1) immediate operation; (2) admit and re-evaluate; or (3) no appendicitis (patient discharged). Based on ultrasonography after clinical evaluation, patients were grouped as positive or negative for appendicitis. Patients in clinical group 1 or those positive on ultrasonographic evidence were destined for operation. Patients in whom ultrasonography gave no evidence of appendicitis were treated according to clinical findings. The results of the study are presented in terms of actual treatment given, although evaluation based on intention to treat would have been more useful, since in a few cases the protocol had been violated. The endpoint of the study was the rate of negative laparotomies, defined as the finding of a normal appendix with no other pathology requiring surgical treatment

Of a total of 366 patients admitted to the study 101 underwent operation. Acute appendicitis was confirmed in 85 patients. Eight patients had other findings requiring surgical treatment (acute cholecystitis and intussusception, two each; perforated diverticulitis, aggressive lipomatosis, adenocarcinoma of the ascending colon, and omental tumour, one each). Eight patients (7·9 per cent) underwent a negative laparotomy.

In 38 of 85 patients (45 per cent) with acute appendicitis the correct diagnosis was missed by the initial clinical examination. The overall sensitivity, specificity and accuracy of clinical diagnosis were 55·3, 94·6 and 84·2 per cent respectively. Positive and negative predictive values were 75·8 and 87·3 per cent respectively. In 18 of 85 patients (21 per cent) with confirmed acute appendicitis the correct diagnosis was missed by ultrasonography. The overall sensitivity, specificity and accuracy of ultrasonographic diagnosis were 78·8, 97·5 and 93·1 per cent respectively. Positive and negative predictive values of ultrasonography were 90·5 and 93·8 per cent respectively

The combined use of clinical examination supported by ultrasonography increased sensitivity, specificity and accuracy to 85·9, 96·4 and 94·0 per cent respectively. The negative laparotomy rate was only 7·9 per cent when ultrasonography was used The authors conclude that ultrasonographic examination provides a useful adjunct to clinical examination in the diagnosis of acute appendicitis.

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Elective splenorenal Warren shunt

K. J. Paquet, A. Lazar, M. A. Mercado and H. A. Gad
Chirurg 1991, **62**: 794–8

Between 1982 and 1990 a total of 399 patients were admitted with recurrent bleeding from oesophageal varices. Injection sclerotherapy constituted the first line of treatment. Patients with early recurrence or uncontrollable bleeding were treated with a Linton–Nachlas tube, and if this was not successful they were subjected to surgical devascularization. Sclerotherapy failure was defined as two or more recurrent episodes of bleeding. Patients in whom sclerotherapy had failed were candidates for elective portosystemic shunting if they met the following selection criteria: liver volume 1000–2500 ml; residual portal blood flow more than 30 per cent; no active or progressive liver cirrhosis; no stenosis of hepatic arterial supply; and Child–Pugh grade A or B

The preferred method for portal decompression was a distal splenorenal shunt, which was technically feasible in 34 of 44 patients (77 per cent). Ten patients with chronic pancreatitis required another method for adequate portal drainage and had a mesocaval shunt. The postoperative mortality rate was 5·9 per cent for splenorenal and 10·0 per cent for mesocaval shunts. The Kaplan–Meier estimate of survival rate was 90 per cent at 1 year and 68 per cent at 8 years for the 34 patients with distal splenorenal shunts. Causes of six late deaths were liver failure (three), peritonitis following spontaneous small bowel perforation, hepatocellular carcinoma and hepatorenal syndrome (one each) Surviving patients were maintained on a diet containing less than 60 g protein and lactulose. None of the survivors developed signs of encephalopathy.

Postoperative complications included one recurrent bleeding episode which was successfully controlled by sclerotherapy All shunts were patent on follow-up angiography at 2 years; one patient had incomplete stenosis. Scintigraphic evaluation of 30 of the 32 surviving patients 1–2 years after operation revealed a liver perfusion index of 20–35 (mean 26) per cent.

Application of strict selection criteria resulted in only 8·5 per cent (34 of 399) of all patients evaluated being deemed eligible for elective distal splenorenal shunting. Results for this group of patients, however, are excellent with only one recurrent episode of bleeding, no encephalopathy and a calculated 8-year survival rate of almost 70 per cent.

The editors invited a commentary on this report (Häring, Berlin). Based on his department's experience with 646 portosystemic shunt operations, the commentator strongly objected to the authors' conclusion that the distal splenorenal shunt represents the 'gold standard' for portal decompression and recommended portocaval shunting. This notion is supported by a low mortality rate of 1·2 per cent in 83 patients classed as Child's grade A and B treated by elective portocaval shunt between 1980 and 1990 and a mortality rate of 6 per cent for emergency portocaval shunting in those classified as Child's grade A A distal splenorenal shunt should be reserved for elective patients of Child's grade B or C.

Gastrointestinal anastomoses using the biofragmentable Valtrac ring. A prospective study

A. Thiede, G Schubert, J. Klima and L. Schmidt
Chirurg 1991; **62**: 819–24

Between March 1989 and December 1990 a total of 150 intestinal anastomoses were performed using a biofragmentable ring composed of 88 per cent (w/w) polyglycolic acid and 12 per cent (w/w) barium sulphate to ensure radio-opacity Anastomoses were performed at a variety of sites including the colon ($n = 109$), small bowel ($n = 11$), stomach, oesophagus and rectum.

Intraoperative problems were frequently encountered: serosal tears ($n = 12$), mucosal prolapse ($n = 11$) and insufficient ring closure ($n = 4$). These posed no major difficulty – serosal tears were oversewn safely or sealed with fibrin glue and mucosal prolapse was corrected by simple resection. None of these events resulted in postoperative complications. No patient had a bleeding complication from the anastomotic site. Technical difficulties were encountered if the colonic wall was thickened or in low anterior resections, since no suitable introducer is available. In four patients the ring could not be applied because the diameter of the bowel lumen precluded its introduction (minimum available diameter 28 mm). Little information was provided concerning the reduction of operating times. It would seem that small bowel anastomoses were performed more rapidly than with standard techniques, while colonic anastomoses required approximately the same amount of time

Postoperative complications related to the ring were recorded in 11 patients and all involved colonic anastomoses. Anastomotic leakage was detected radiologically in six patients, and three of these presented with supporting clinical evidence Two patients developed fistulae following colonic resection; these were apparently related to the use of drains. No patient required reoperation Two patients died in the postoperative period, but these deaths (from myocardial infarction and splenic artery erosion) were not attributable to the use of the ring.

In all patients the ring fragmented and was passed between days 12 and 30 after operation. There was no instance of bowel obstruction, and passage of the ring or its fragments occurred unnoticed in 98 per cent of patients.

Long-term radiological studies were performed in 30 patients at 6–12 months. All anastomoses were patent without evidence of stenosis or leakage. In 78 per cent of these patients the site of the anastomosis could not be distinguished radiologically from the remainder of the colon.

Ch. Herfarth
Editor
Der Chirurg

Br. J. Surg. 1992, Vol 79, April, 293–299

Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970

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In this review of English language publications from 1970, 5-year survival rates after surgery for gastric cancer have been analysed. While the proportion of patients coming to operation has fallen from 92 per cent before 1970 to 71 per cent by 1990, the proportion of operated patients undergoing resection has increased from 37 per cent before 1970 to 48 per cent before 1990. This change suggests improved preoperative staging leading to better patient selection for operation. The 5-year survival rate following all resections has increased significantly from 20·7 per cent before 1970 to 28·4 per cent before 1990, an increase of 7·7 per cent (95 per cent confidence interval 7·1–8·3 per cent). The 5-year survival rate following curative or radical resection has risen from 37·6 to 55·4 per cent over the same period, an increase of 17·8 per cent (95 per cent confidence interval 17·1–18·5 per cent). It is likely that this improvement has contributed to the decrease in the mortality rate from gastric cancer. Comparison of Japanese series with others suggests that diagnosis and treatment of the disease at an earlier stage will result in an even greater increase in 5-year survival rates outside Japan. Of the papers studied, 56 per cent were excluded from analysis, the majority because the data provided about 5-year survival rates were insufficient or the survival calculations inappropriate. Results of survival after operations for gastric cancer should be calculated and presented in a standardized manner.

Mortality rates from gastric cancer have been falling throughout the world over the past 30 years[1,2]. It has been shown that, in Scotland, while the mortality rate continues to fall, the decline in incidence has been much less marked[3]. Indeed, the standardized incidence rate in Scotland in the decade to 1980 showed only a marginal decline, which for women was not statistically significant. As the number of operations for gastric cancer in this area has remained constant over this period, the hypothesis has been examined that the decline in mortality rate, in the face of a steady surgical workload and incidence, might be the result of better surgical treatment.

In an earlier review[4] a progressive decline was shown in operative mortality rates in English language series reporting operations in successive decades to 1970, 1980 and 1990. The aim of the current review was to ascertain whether the 5-year survival rate has improved in series reported since 1970 and, if so, to establish whether these improved surgical results might have contributed to the decline in mortality rate

Methods of analysis

All English language publications from 1970 on the surgical treatment of gastric cancer were reviewed. The list of publications was obtained from three large computer databases – Medline, Excerpta Medica (which began in 1974) and the bibliography on stomach cancer (based on Medlars and searched by the Japan Information Centre of Science and Technology). Of the 225 papers reviewed 125 were excluded, leaving 100 for analysis. The reasons for exclusion are shown in *Table 1.*

The series were analysed for 5-year survival rates. Only those in which follow-up was for a minimum of 5 years or in which a life-table analysis had been included were considered. The series were then grouped into those which had closed before 1970, before 1980 and before 1990, respectively, to permit a comparison of the trends through time.

Many series included a mixture of patients who had undergone a palliative operation with those thought to have undergone curative surgery. As no 5-year survival would be expected in the former group, these series were analysed to show separately the 5-year survival rate in all patients, in patients undergoing resection, and in those undergoing curative or radical resection.

The mean 5-year survival rates were calculated by totalling

Table 1 *Exclusion of papers from review*

Reason for exclusion	No of papers excluded
No data or insufficient data on 5-year survival	39
Adjuvant therapy included	29
Operative mortality rate excluded from survival data	14
Included in another paper	11
Review	9
Combined oesophageal/gastric cancers	5
Cancer after previous gastric surgery	4
Multiple early gastric cancers	3
Untraceable	5
Other	6
Total	125

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all patients alive or expected to be alive at 5 years in all studies and expressing these as a percentage of the numbers of patients entering the studies.

Results

The numbers of series closing in the three decades are shown in *Table 2*. Of the 23 series closing before 1970, ten provided data on 5-year survival for curative or radical resection. For the 35 series closing before 1990, 23 gave survival analyses for curative or radical resection. The results in terms of 5-year survival for all operations, all resections, and curative or radical resections, together with operative mortality rates over the three decades studied[5–104], are shown in *Tables 3–5*. The mean 5-year survival rate in the three decades studied for all operations, for all resections, and for curative and radical resections is shown in *Table 6*. Five-year survival rates following all resections increased significantly between series closing before 1970 and those ending before 1990, by 7·7 per cent (95 per cent confidence interval (c.i.) 7·1–8·3 per cent). The 5-year survival rate following curative or radical resection rose significantly from 37·6 per cent in series closing before 1970 to 55·4 per cent in those ending before 1990, an increase of 17·8 per cent (95 per cent c.i. 17·1–18·5 per cent).

The differences between Japanese and non-Japanese series are shown in *Table 7*. The resection rate was much higher among Japanese patients (93·1 *versus* 35·2 per cent) and the mean 5-year survival rate after curative resection was 60·5 per cent compared with 39·4 per cent for non-Japanese patients, a difference of 21·1 per cent (95 per cent c.i. 19·7–22·6 per cent).

For the combined series reviewed, the mean 5-year survival rate was 52·2 per cent after curative or radical resection.

Discussion

In a review of published series such as this, several problems must be considered before clear conclusions can emerge. There was considerable variation in the method of presentation of results. Many of the series were excluded because they failed to meet simple criteria which would allow a valid assessment of 5-year survival. A frequent reason for exclusion was failure

Table 2 *Series analysed in the three decades to 1970, 1980 and 1990*

	No. of series	All operations	All resections	Curative or radical resections
Before 1970	23	16	9	10
Before 1980	42	20	10	27
Before 1990	35	21	15	23
Total	100	57	34	60

Table 3 *5-Year survival rates in patients with gastric cancer undergoing operation in series closing before 1970*

								5-Year survival rate (%)		
Reference	Years studied	Country of study	No studied	All operations	All resections	Curative or radical resections	Operative mortality rate (%)	All operations	All resections	Curative or radical resections
Sharma[5]	1961–1965	India	377	276 (73)	135 (36)	—	13·4‡	3·43	—	—
Fielding *et al.*[6]	1960–1969	UK	13 228	—	3523 (27)	—	5·5*	3·7¶	(70·4¶ early gastric cancer)	14·6¶
Crumb *et al*[7]	1956–1969	USA	79	79 (100)	—	19 (24)	—	5·1§	—	21§
Thomson *et al.*[8]	1961–1964	UK	1 198	1198 (100)	827 (69)	172 (14)	—	5·2§	—	25§
Costello *et al.*[9]	1960–1969	UK	226	218 (96)	150 (66)	—	—	8·5§	—	18#
Lulu and Ochoa[10]	1954–1970	USA	100	87 (87)	72 (72)	46 (46)	20·7*	9	—	19·6
Paymaster *et al*[11]	1941–1968	India	763	—	335 (44)	—	—	9·5	—	—
Svennevig and Nysted[12]	1959–1968	Norway	220	149 (68)	94 (43)	71 (32)	—	10§	—	26·8§
Seppala[13]	1957–1959	Finland	140	95 (68)	60 (43)	—	—	11§	26·6§	—
Buchholtz *et al.*[14]	1962–1966	USA	201	187 (93)	131 (65)	96 (48)	—	11§	—	24§
Cassell and Robinson[15]	1948–1962	UK	854	663 (78)	390 (46)	—	15·7†	11·2§	19§	—
Moore[16]	1941–1970	Canada	1 030	874 (85)	466 (45)	—	—	11·7§	26·3§	—
Nielsen *et al.*[17]	1955–1964	Denmark	385	352 (91)	193 (50)	161 (42)	14	12§	24§	30¶
Mine *et al*[18]	1955–1963	Japan	438	408 (93)	277 (63)	—	8·8	14·4§	27·5§	—
Desmond[19]	1944–1970	UK	1 168	—	—	—	—	15	20	—
Kenter and Zwaveling[20]	1958–1968	Netherlands	238	—	128 (54)	75 (32)	18·5*	16·2	—	—
Inberg *et al.*[21]	1946–1965	Finland	1 963	1138 (58)	524 (27)	—	—	19·6	—	23·8
Cantrell[22]	1953–1957	UK	165	165 (100)	165 (100)	35 (21)	—	—	14·6§	46§
Hawley *et al.*[23]	1951–1955	UK	205	190 (93)	190 (93)	—	25‡	—	19·4	—
McNeer *et al*[24]	1950–1964	USA	94	94 (100)	94 (100)	—	17‡	—	23·4§	—
White *et al*[25]	1953–1966	USA	242	—	—	242 (100)	7·1	—	—	18·6§
Soga *et al.*[26]	1961–1970	Japan	698	—	—	530 (76)	—	—	—	150·6§
Yamada *et al.*[27]	1965–1970	Japan	195	—	—	195 (100)	—	—	—	96¶

Values in parentheses are percentages. *30 Days; †3 months, ‡other, including in hospital, §crude survival, #life-table analysis, ¶corrected life-table analysis

Table 4 *5-Year survival rates in patients with gastric cancer undergoing operation in series closing before 1980*

								5-Year survival rate (%)		
Reference	Years studied	Country of study	No studied	All operations	All resections	Curative or radical resections	Operative mortality rate (%)	All operations	All resections	Curative or radical resections
Nelson and Collier[28]	1970–1975	Australia	229	187 (82)	128 (56)	79 (34)	—	4·8§	—	13·9§
Beradi *et al.*[29]	1963–1971	USA	41	41 (100)	29 (71)	6 (15)	14 6*	2 4	—	—
Bloss *et al.*[30]	1946–1976	USA	37	30 (81)	21 (57)	—	—	5·4§	—	—
Weed *et al.*[31]	1958–1978	USA	265	249 (94)	—	69 (26)	—	5·5#	—	26#
Inberg *et al.*[32]	1946–1972	Finland	2590	1634 (63)	804 (31)	—	10·5*	5·8§	19 9	—
Dupont *et al.*[33]	1948–1973	USA	1497	1228 (82)	718 (48)	—	26·5*	7·4§	—	24§
Hughes *et al*[34]	1950–1973	Australia	246	241 (98)	241 (98)	70 (28)	–	8·1§	—	28·6§
Armstrong and Dent[35]	1974–1975	South Africa	227	201 (89)	103 (45)	42 (18)	6·8	8·5§	—	45§
Bizer[36]	1972–1976	USA	171	146 (85)	91 (53)	48 (28)	13·7	10	—	20·5
Adashek *et al.*[37]	1956–1975	USA	501	369 (74)	222 (44)	132 (26)	13	10#	—	32#
Stewart *et al.*[38]	1970–1974	New Zealand	1891	—	737 (39)	473 (25)	19*	10 2¶	24·7¶	—
Rheault *et al.*[39]	1948–1978	Canada	64 early gastric cancer	—	—	60 (94)	1·7	12·2§	—	95·3§ early gastric cancer
Viste *et al.*[40]	1976–1980	Norway	206	187 (91)	105 (51)	65 (32)	15 5*	13#	—	40§
Bako *et al.*[41]	1969–1973	Canada	467	—	—	233 (50)	—	13#	—	24#
Søreide *et al.*[42]	1972–1977	Norway	274	242 (88)	179 (65)	—	—	13#	—	—
Ribeiro *et al.*[43]	1970–1977	Portugal	242	209 (86)	94 (39)	85 (35)	—	16·1#	—	42·6#
Hoerr[44]	1950–1972	USA	478	454 (95)	—	222 (46)	10 2	17·7§	—	—
Zillotto *et al.*[45]	1960–1978	Brazil	189	166 (88)	—	85 (45)	—	19·8§	—	38·8§
Maetani *et al.*[46]	1966–1973	Japan	1026	—	896 (87)	—	—	35·4¶	—	—
Yamada *et al.*[47]	1965–1977	Japan	2421	—	1952 (81)	1502 (62)	2·4	43·6¶	—	65 6¶
Bozzetti *et al.*[48]	1965–1980	Italy	294	246 (84)	61 (21)	—	8·1	—	6¶	—
Schrock and Way[49]	1940–1975	USA	87	—	87 (100)	59 (68)	15†	—	9§	13 7§
Korenaga *et al.*[50]	1964–1978	Japan	281	—	281 (100)	—	—	—	17·4#	36·7§
Bozzetti *et al.*[51]	1965–1980	Italy	143	—	143 (100)	—	15·4‡	—	19¶	—
Paolini *et al.*[52]	1971–1978	Italy	110	91 (83)	73 (66)	—	18	—	21 9	—
Haraguchi *et al*[53]	1975–1980	Japan	275	—	—	—	—	—	23§	—
Stark and Sauter[54]	1970–1979	USA	66	—	66 (100)	—	10	—	25§	—
Shiu *et al.*[55]	1955–1975	USA	213	—	—	213 (100)	21	—	—	16·9
Shiu *et al*[56]	1960–1980	USA	1464	883 (60)	—	210 (14)	—	—	—	30§
Inberg *et al.*[57]	1956–1977	Finland	291	291 (100)	—	291 (100)	13·4*	—	—	33#
Yap *et al*[58]	1950–1974	Phillipines	465	—	465 (100)	235 (51)	2·8	—	—	35·7§
Baba *et al.*[59]	1975–1980	Japan	142	—	—	142 (100)	—	—	—	94 4#
Diehl *et al.*[60]	1970–1980	USA	164	150 (91)	82 (50)	45 (27)	6	—	—	40#
Salo *et al.*[61]	1975–1980	Finland	438	389 (89)	—	59 (13)	5 (after curative resection)	—	—	42§
Gennari *et al*[62]	1965–1979	Italy	402	—	—	402 (100)	—	—	—	49·8#
Oohara *et al.*[63]	1958–1980	Japan	406	—	288 (71)	190 (47)	16 5	—	—	51 5
Soga *et al*[64]	1961–1980	Japan	1342	—	—	1011 (75)	—	—	—	57·8§
Faivre *et al*[65]	1976–1980	France	381	238 (62)	176 (46)	153 (40)	—	30·7§	—	36 0¶
Imanaga and Nakazato[66]	1964–1973	Japan	1628	1628 (100)	1298 (80)	995 (61)	2·8*	—	—	63 7¶
Gebhardt *et al*[67]	1970–1979	Germany	130	—	—	130 (100)	8	—	—	82¶
Abe *et al.*[68]	1967–1979	Japan	140	—	—	140 (100) early gastric cancer	—	—	—	96 2¶ early gastric cancer
Henrichsen *et al.*[69]	1949–1971	Denmark	49	—	49 (100)	—	13·5*	—	46§	—

Values in parentheses are percentages. *30 Days; †3 months; ‡other, including in hospital; §crude survival; #life-table analysis; ¶corrected life-table analysis

Table 5 *5-Year survival rates in patients with gastric cancer undergoing operation in series closing before 1990*

								5-Year survival rate (%)		
Reference	Years studied	Country studied	No. studied	All operations	All resections	Curative or radical resections	Operative mortality rate (%)	All operations	All resections	Curative or radical resections
Matley *et al*[70]	1980–1985	South Africa	37	—	—	—	—	2 7§	—	—
Allum *et al.*[71]	1957–1981	UK	31 716	17 565 (55)	9247 (29)	6588 (21)	18·8*	5¶	—	—
Mayers *et al.*[72]	1953–1983	USA	255	215 (84)	—	65 (25)	11*	62#	—	24#
Sjostedt and Pieper[73]	1972–1982	Sweden	141	—	—	48 (34)	27 9 (after curative resection)	7	—	25
Breaux *et al.*[74]	1948–1983	USA	213	155 (73)	96 (45)	55 (26)	25·8	8·9#	24 8#	—
Carmalt *et al*[75]	1974–1987	Australia	511	448 (88)	284 (56)	162 (32)	6·5	12·3§	—	43
McBride and Boddie[76]	1944–1984	USA	2 062	1 443 (70)	1216 (59)	165 (8)	16	12·5	—	75 (stage I)
Lygidakis[77]	1964–1983	Netherlands	389	313 (80)	258 (66)	159 (41)	5·1	14·7§	18·2§	34 6§
Carter *et al*[78]	1974–1982	USA	31	—	—	—	—	15	—	100# (early gastric cancer cases only)
Akoh *et al*[79]	1975–1985	UK	280	183 (65)	129 (46)	—	15	15¶	28¶	—
Hartley *et al.*[80]	1973–1981	Australia	313	244 (78)	158 (50)	133 (42)	8·9‡	15·8¶	31·3¶	35·7¶
Bittner *et al.*[81]	1969–1984	Germany	186	—	—	—	13 4	15·9	—	—
Lindahl *et al.*[82]	1974–1984	Norway	294	—	171 (58)	141 (48)	2 8*	16	—	40#
Moreaux and Msika[83]	1964–1985	France	114	82 (72)	76 (67)	58 (51)	2 6	18·5§	29¶	40¶
Gall and Hermanek[84]	1969–1982	Germany	1 636	—	1104 (67)	719 (44)	12·2‡	20·8	—	47
Irvin and Bridger[85]	1979–1986	UK	122	111 (91)	78 (64)	—	9*	20¶	—	60¶
Cady *et al*[86]	1967–1982	USA	211	176 (83)	122 (58)	72 (34)	2 8‡	21	36	58
Meyer *et al.*[87]	1968–1987	Germany	1 510	—	1135 (75)	—	12·4	22 6	29·8	—
Msika *et al.*[88]	1967–1985	France	156	—	110 (71)	86 (55)	10	25	36#	44
Secco *et al.*[89]	1968–1983	Italy	209	209 (100)	—	—	—	25 4	—	—
Nakajima and Nishi[90]	1946–1986	Japan	8 786	—	7872 (90)	5862 (67)	1 9*	37·4	—	59·4¶
Bringaze *et al*[91]	1963–1983	USA	327	—	327 (100)	153 (47)	—	—	18·8	100¶ (early gastric cancer)
de Calan *et al.*[92]	1968–1983	France	91	84 (92)	57 (63)	28 (31)	16	—	20¶	40¶
Saario *et al*[93]	1975–1982	Finland	52	—	—	—	—	—	21 2§	—
Ellis *et al*[94]	1970–1988	USA	149	—	127 (85)	104 (69)	6·8	—	22 4¶	—
Yan and Brooks[95]	1958–1982	USA	196	—	153 (78)	87 (44)	4 6	—	24·9	36·2¶
Gouzi *et al.*[96]	1980–1985	France	169	—	169 (100)	—	—	—	48#	—
Gardiner *et al.*[97]	1976–1988	UK	30	—	—	—	0	—	68	—
Cunningham *et al.*[98]	1974–1984	UK	328	277 (84)	160 (49)	128 (39)	—	—	—	24#
Wyatt *et al.*[99]	1968–1984	UK	325	—	—	115 (35)	5 3	—	—	40§
Chao-Hong[100]	1960–1982	China	1 399	—	1105 (79)	834 (60)	2·1*	—	—	53·8
Boku *et al.*[101]	1975–1986	Japan	521	521 (100)	521 (100)	521 (100)	—	—	—	54·5
Green *et al*[102]	1960–1984	USA	63	—	—	63 (100)	—	—	—	97 (early gastric cancer)
Houghton *et al*[103]	1965–1984	UK	35	34 (97)	31 (89)	30 (86)	5 7	—	—	92¶
Kawaura *et al*[104]	1972–1982	Japan	70	—	—	—	4 3*	—	—	35·7

Values in parentheses are percentages. *30 Days; †3 months, ‡other, including in hospital, §crude survival, #life-table analysis; ¶corrected life-table analysis

to follow all patients for a minimum of 5 years where a crude survival rate had been calculated by the direct method. Another common error was to exclude from survival analysis those patients who died in the immediate postoperative period (and were thus included under operative mortality). Failure to supply figures from which life-table graphs were calculated usually precluded the inclusion of such series in this review. We recommend that series deficient in these respects should not be presented or accepted for publication.

A further problem besetting a review which attempts to assess changes in treatment or outcome over a defined period is that many series cut across the decades, which inevitably have to be chosen arbitrarily. For example, in a series closing in 1981 the overwhelming majority of patients will have been

Table 6 *The three decades compared*

	Before 1970	Before 1980	Before 1990
No. of series	23	42	35
Total patients	24 207	22 652	52 927
Operation (%)	92·3	83·5	71·0
Resection (%)	37·1	52·7	47·7
Curative or radical resection (%)	9·0	32·9	31·1
Mean 5-year survival rate (%)			
After resection	20·7	21·2	28·4
After curative or radical resection	37·6	52·0	55·4

Table 7 *Japanese and non-Japanese series compared*

	Japanese	Non-Japanese	Total
No. of series	15	85	100
Total patients	19 048	80 738	99 786
Operation (%)	99·8	74·1	79·0
Resection (%)	93·1	35·2	46·3
Curative or radical resection (%)	58·6	17·8	25·6
Mean 5-year survival rate (%)			
After curative or radical resection	60·5 (6736 of 11 139)	39·4 (2836 of 7205)	52·2 (9572 of 18 344)

operated on in the 1980s and perhaps even in the 1970s, yet for the purposes of this study such a series would have been included in those closing before 1990. The dates at which all series opened and closed have been indicated and we consider that this factor does not substantially affect the trends which have been demonstrated.

Over the period covered in this review the outlook for patients with gastric cancer has improved. The proportion coming to operation has fallen from 92 per cent before 1970, to 84 per cent before 1980, to 71 per cent before 1990. We believe that this demonstrates improved patient selection. The greater use of preoperative investigations to stage the disease appears to have led to a decline in 'open and close' laparotomies. This is confirmed by the increasing proportion of patients coming to resection (37 per cent before 1970 increasing to 48 per cent before 1990) and the dramatic rise in patients undergoing curative or radical resection (from 9 per cent before 1970 to 31 per cent before 1990). Survival rates in patients with gastric cancer have also improved.

A decline in operative mortality rates over the past 30 years has previously been demonstrated[4]. This review has shown an improvement in 5-year survival in published series over the same period. The 5-year survival rate after resection has increased significantly from 20·7 per cent before 1970 to 28·4 per cent before 1990, and following curative or radical resection from 37·6 per cent before 1970 to 55·4 per cent before 1990. This is not caused merely by the inclusion of Japanese series; when these are excluded from analysis the 5-year survival rate after resection is 23·4 per cent, and after curative or radical resection 39·4 per cent.

The analysis of all series published in English in this way is rendered difficult because of differing methods of calculating and reporting survival rates. To overcome this problem series in which the data were inadequate have been excluded. The percentage 5-year survival figures have been calculated by adding together all patients reported alive at 5 years and expressing these as a percentage of all those entering the series. We recommend to authors and editors that survival rates in published series should be calculated using life-table analysis and should include those patients who die in the immediate postoperative period.

Separate survival rates should be calculated for those patients undergoing curative resection, palliative resection, bypass and laparotomy alone. Similarly, separate rates should be recorded for distal gastrectomy, total gastrectomy and thoracoabdominal oesophagogastrectomy. Reports should also contain analysis of tumour stage, using the UICC (Union Internacional Contra la Cancrum) classification.

This review has shown that the outlook for patients with gastric cancer has improved over the past 30 years. It seems likely that a combination of earlier diagnosis, better preoperative staging, more radical surgery and better perioperative care has contributed to this improvement. If the marginal decline in the incidence of gastric cancer and its associated steady surgical workload which has been shown in Scotland is a global phenomenon, it seems likely that improvements in surgical diagnosis and technique have indeed contributed to the decline in the mortality rate from this disease. These findings should give added impetus to efforts to diagnose gastric cancer early and to treat it by radical resection.

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Role of selective decontamination in surgery

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Aspects of selective decontamination as an antibiotic prophylaxis in general surgery are discussed with respect to the respiratory tract and wound infection. The high rate of nosocomial infection encountered in surgical patients, who experience up to 71 per cent of all such infection, is considered. The infection rate increases to 70–80 per cent after 1 week in the surgical intensive care unit, while the infection-related mortality rate rises to up to 60 per cent. The endogenous origin of nosocomial infection suggests the importance of maintaining colonization resistance to prevent colonization with Gram-negative micro-organisms, especially using selective decontamination which eliminates potentially pathogenic micro-organisms while leaving colonization resistance intact. Selective decontamination has proved effective in decreasing infection rates by 50–80 per cent, and is especially successful in respiratory tract infection. Possible adverse effects and future indications for selective decontamination are discussed.

The prophylactic use of antibiotics in surgery is mainly concerned with the prevention of postoperative wound and deep infection, it is generally accepted as being effective when the proper antibiotic is given in the right dosage for a short period around the time of operation[1–3], thereby providing effective tissue levels of the drug at the time of surgery. Even patients undergoing clean procedures such as herniorrhaphy and breast surgery may benefit from antibiotic prophylaxis, as indicated in a large multicentre trial (48 per cent fewer infections compared with a placebo group)[4]. Not surprisingly, 40 per cent of surgical patients receive prophylactic antibiotics, accounting for 30 per cent of all in-hospital antibiotic use[5]. Approximately 20–30 per cent of all hospital patients receive antibiotics during their stay, but in an inappropriate dose or for an inappropriate duration in 31–62 per cent of cases[2,6,7]. Transfer of resistance among micro-organisms occurs especially on mucosal surfaces in the digestive tract or on the skin[8,9] and the inappropriate use of antibiotics is one of the causes of the increasing drug resistance seen in hospital flora. For this reason each new prophylactic regimen should be adopted only reluctantly in clinical practice, with maximal surveillance for the possible development of resistance.

Epidemiology of nosocomial infection and the magnitude of the problem

Nosocomial infections are those arising after 48 h of admission, caused mostly by Gram-negative micro-organisms, and distributed through the various sites shown in *Table 1*. Despite attempts to prevent wound infection by perioperative antibiotic prophylaxis, such infection accounts for 40 per cent of all nosocomial infections in surgical patients[9–13] Nosocomial infection affects 71 per cent of surgical patients, who represent 41 per cent of all hospital admissions. Surgical patients have a 14 per cent risk of developing a lower respiratory tract infection compared with a 3 per cent risk for all admissions[10]. Approximately 33–45 per cent of nosocomial infections occur in the intensive care unit (ICU), which comprises only 8 per cent of hospital beds[14], and after 1 week of admission to the ICU 70–80 per cent of patients have (predominantly) Gram-negative infections, leading to an infection-related mortality rate of up to 60 per cent[11,12,15–18].

Although wound and urinary tract infections occur in greater numbers (*Table 1*), respiratory tract infection is of more importance because of its higher related mortality rate. More than 60 per cent of respiratory infections occur in patients in the ICU, with mortality rates of 33 per cent in patients with a pneumonia due to Gram-negative bacilli and 70 per cent in those due to *Pseudomonas* spp.[7,10,19].

Despite progress in modern medicine and surgical technique, efforts to prevent these life-threatening complications have been disappointing. Control of these infections proves to be complex because on admission more than 50 per cent of patients are already colonized with the micro-organisms that subsequently cause their infection[20], and the relationship between oropharyngeal colonization and respiratory tract infection is an intimate one[21,22] – important evidence for the endogenous aetiology of nosocomial infection[23]. Endogenous infection is preceded by colonization with the causative micro-organism; colonization is the presence of the bacterium in consecutive cultures without signs of infection.

Colonization and colonization resistance

When admitted to hospital, a patient's normal microbial flora may be quickly replaced by hospital-acquired Gram-negative bacilli (colonization), which are increasingly antibiotic-multiresistant[5,12,21]. These potentially pathogenic micro-organisms (PPMs) which cause infection when resistance is impaired are listed in *Table 2* Critically ill and immunocompromised patients will be colonized within a short time of admission[21,24], while healthy individuals are hardly ever

Table 1 *Site of nosocomial infection in surgical patients*

Site	Frequency of involvement (%)
Urinary tract	42
Wound	40
Respiratory tract	14
Blood (septicaemia)	4

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Table 2 *Potentially pathogenic micro-organisms*

Gram-negative species
  Escherichia coli
  Klebsiella
  Serratia
  Proteus
  Enterobacter
  Citrobacter
  Pseudomonas
  Haemophilus influenzae
  Acinetobacter
  Branhamella catarrhalis
  Neisseria
Gram-positive species
  Staphylococcus aureus
  Streptococcus pneumoniae
  Enterococci
Yeasts
  Candida albicans

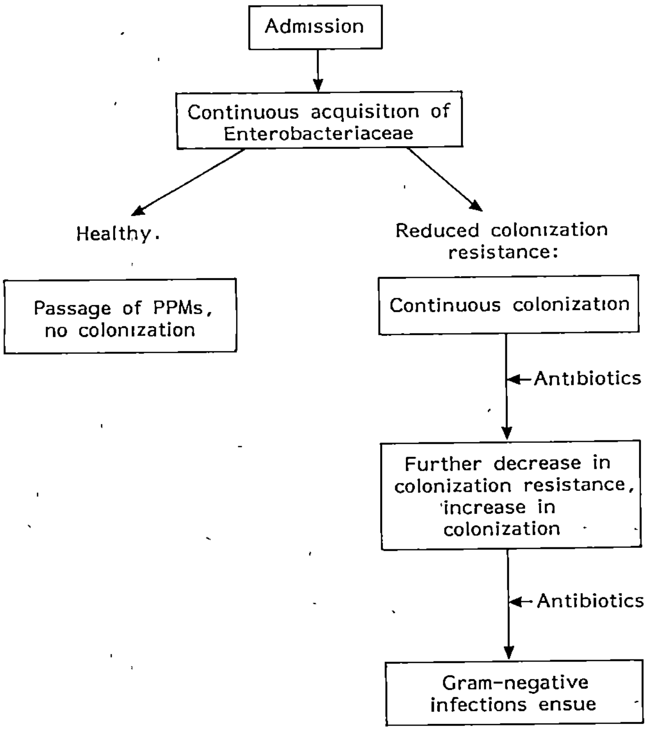
Admission
Continuous acquisition of Enterobacteriaceae
Healthy.
Reduced colonization resistance:
Passage of PPMs, no colonization
Continuous colonization
Antibiotics
Further decrease in colonization resistance, increase in colonization
Antibiotics
Gram-negative infections ensue

Figure 1 *Interaction between potentially pathogenic micro-organisms (PPMs) and the host, and the influence of antibiotics*

colonized with Gram-negative flora (*Figure 1*). Colonization is, therefore, frequently encountered in patients in the ICU, in whom several risk factors can be recognized: endotracheal intubation, coma, hypotension and acidosis[25], length of admission[26,27], advancing age[28], number of invasive procedures[11,27,28] and use of immunosuppressive agents and antibiotics (of whatever spectrum)[25,29,30].

After experiments in mice, van der Waay *et al.*[31] introduced the concept of colonization resistance. They described the elimination of Enterobacteriaceae from the gut and a prolonged prevention of recolonization by these micro-organisms using selective oral antibiotics. They considered colonization resistance as the first host defence against colonization with Gram-negative micro-organisms, consisting of a physiological part (*Table 3*) and a microbiological part, the latter predominantly constituted by the anaerobic flora which oppose aerobic flora mainly by competition for food. Others confirmed the pivotal role of anaerobes in colonization resistance, but thought a polymicrobial flora could maximize colonization resistance[32,33]. Barza *et al.*[34] studied colonization resistance in human volunteers, and while they were able to confirm the devastating effect of broad-spectrum antibiotics on colonization resistance, they could not prove that anaerobic microbes had a role to play in such resistance. Patients with reduced defence mechanisms (*Table 4*) may benefit from an optimal microbiological colonization resistance which is produced by colonization resistance-indifferent antibiotics, i.e. antibiotics that leave those anaerobic flora thought to be responsible for colonization resistance undisturbed (*Table 5*).

Prevention of colonization by antibiotic prophylaxis

Efforts to prevent colonization using inadequate antibiotic regimens are disappointing[35] and result in colonization with resistant strains[36,37], causing persistent infections with high mortality rates. These infections, occurring during antibiotic therapy and caused by PPMs resistant to the antibiotics used, are known as superinfections. As early as 1947 Weinstein[30] had ascribed superinfections with resistant Gram-negative PPMs to the disturbance of the microbial equilibrium resulting from the use of antibiotics, and in 1970 Price and Sleigh[38] were able to end an epidemic of infections with multiresistant *Klebsiella aerogenes* by the withdrawal of ampicillin and cloxacillin, drugs in use in their ICU for a period of 2 years. They thought the previously sensitive microbial flora was quickly replaced by nosocomial Gram-negative bacilli resistant to the antibiotics in use, resulting in superinfections. By discontinuing all antibiotics the normal flora could be restored and colonization prevented by the restoration of colonization resistance.

Attempts to eradicate PPMs by total decontamination of the gut and skin in combination with complete isolation seemed worthwhile in granulocytopenic patients, but needed strict patient compliance, were expensive, and only 30–40 per cent of cases proved successful[39–41]. Again the danger of acquisition,

Table 3 *Physiological factors responsible for colonization resistance*

Integrity of epithelial and mucosal lining
Desquamation of epithelial and mucosal cells
Saliva and mucus
Secretory immunoglobulin A
Normal swallow and cough reflexes
Chewing and peristalsis, normal defaecation
Presence of anaerobic flora in the gut

Table 4 *Factors adversely affecting colonization resistance*

Irradiation
Chemotherapy, immunosuppressive agents
Stasis of food and mucus, bacterial overgrowth
Intubation and mechanical ventilation
Aspiration, regurgitation
Bowel dysfunction or retention

Table 5 *Antibiotics indifferent to colonization resistance*

Oral
  Polymyxin E
  Doxycycline
  Tobramycin
  Quinolones
  Co-trimoxazole
  Trimethoprim
Intravenous
  Cefotaxime
  Ceftazidime
  Cefuroxime
  Aminoglycosides
  Quinolones
  Co-trimoxazole
  Trimethoprim

colonization and overgrowth of resistant micro-organisms was increased in the unsuccessful cases. The concept of colonization resistance made it possible to introduce a novel method of infection prevention, named selective decontamination[8,31].

Selective decontamination

Selective decontamination has been in use since the early 1980s in patients with granulocytopenia, with promising results[42,43]. Subsequently, its use in patients in the ICU has become the subject of interest. Stoutenbeek *et al.*[44] were the first to study selective decontamination using a modified regimen in patients with trauma in the ICU and who had been intubated for more than 5 days. They used a combination of non-absorbable antibiotics to reach high topical levels in the oropharynx (paste) and gut (suspension), thus minimizing the risk of resistance. Nevertheless, a considerable number of infections still occurred, mainly because the patients suffered from primary community-acquired respiratory tract infections, caused by Gram-positive micro-organisms, which occurred within 48 h of admission. With the addition of systemic cefotaxime in the first days of treatment, the rate of respiratory tract infection declined from 59 to 8 per cent and the overall infection rate dropped from 81 to 16 per cent[45]. The use of cefotaxime may be discontinued when adequate decontamination has occurred, as indicated by surveillance cultures (no PPMs grown); this systemic antibiotic serves as a protection against early (primary) infection during the first days when selective decontamination has not yet been fully established. Others have changed antibiotic components in the originally described regimen[44] (*Table 6*), with similar effects on the reduction of infection (*Table 7*). In chosing antibiotics for use in selective decontamination, faecal adsorption (as described for polymyxin[56] and the quinolones[57]) has to be considered because this influences free drug concentration on the colonic mucosa. The parenteral administration of metronidazole, in general use in gastro-intestinal surgery for prophylaxis of wound infection, is in this regard permitted because the intraluminal drug concentration is too low to affect colonization resistance[58].

Table 6 *Selective decontamination regimens*

Regimen	Reference nos	Enteral (mg/day) P	T	N	A	Systemic (mg/day) C	Tr
Enteral, oropharyngeal and systemic antibiotics*							
PTAC	44, 46, 50, 53	100	80	—	500	500	—
	54	100	80	—	500	1000	—
	47†	200	80	—	500	500	—
	51‡	200	80	—	500	500	—
PNAC	49	200	—	50	500	500 × 3	—
PNATr	48	200	—	50	500	—	500
Only enteral antibiotics							
PTA	52§	100	80	—	500	No information	
Only oropharyngeal antibiotics							
PTA	55						

P, polymyxin E; T, tobramycin, A, amphotericin B; N, norfloxacin, C, cefotaxime; Tr, trimethoprim. *All regimens given four times a day starting on admission day (except for study 51), systemic prophylaxis was given for 4 days (except for study 47). All studies except 52 achieved oropharyngeal decontamination by a 2 per cent mixture of the enteral antibiotics in orabase; †cefotaxime for 5–7 days; ‡regimen started 3 days before operation, §amphotericin B in study as well as control groups, 2 per cent povidone–iodine lozenge instead of oropharyngeal paste

The use of selective decontamination has proven to be an effective method of retaining colonization resistance in critically ill patients and has led to a reduction of the offensive load of Gram-negative nosocomial PPMs, thereby reducing life-threatening infections.

Practical use of selective decontamination

The authors have introduced the induction of selective decontamination before oesophageal resection and one-stage reconstruction, and have reported an adequate decontamination within 3–4 days[51], in contrast to others[44,47] who needed 7–10 days to decontaminate the gastrointestinal tract. This is probably the result of functional gut in our patients, in

Table 7 *Selective decontamination trials and results. all infections and the subgroup of pneumonia*

Reference no.	Design	Infections	Infection rate (%) Control group	Study group	*P*	Mortality rate (%) Control group	Study group	Subgroup	*P*
44	Historical	All	81	16	<0·001	—	—		
		Pn	59	8	<0·001				
46	Historical	All	24	10	<0·05	24	24		
						3	0	Trauma	<0·05
47	Randomized	All	81	39	<0·001	32	28		
						17	4	Infection-related	<0·05
48	Randomized	All	77	52	<0·05	54	31		<0·05
		Pn	44	6	<0·001	15	0	Septicaemia	<0·05
49	Randomized	Pn	62	6	<0·001	10	12		
50	Historical	Pn	42	6	<0·05	—	—		
51	Randomized	All	55	21	<0·001	3	5		
		Pn	14	2	<0·05				
52	Double blind, placebo controlled	Pn	8	0	<0·05	18	12		
						20	4	⩾7 days	<0·05
53	Double blind, placebo controlled	Pn	45	10	<0·001	47	38		
						74	36	Cardiac surgery	?
54	Historical	All	83	33	<0·05	42	40		
		Pn	42	7	<0·05				
55	Randomized double blind, placebo controlled	Pn	73	0	<0·001	30	33		

Pn, pneumonia

combination with the effects of mechanical bowel preparation. With this preoperative start, even patients with a short stay in the ICU and an immediately compromised colonization resistance may benefit from selective decontamination.

Questions have arisen about the necessity of the different components in the regimen. Some have used systemic antibiotics to protect patients against primary infection[45], while others have reported a significant decrease in the frequency of pneumonia with oropharyngeal[55] or enteral[52] application alone. However, there is often no clear information about[55], or there is no difference in[52], the total number of infected patients, or information is incomplete about the therapeutic use of systemic antibiotics in the first days of treatment[52]. The possibility of eradicating an epidemic of infection with multiresistant PPMs has been raised, but with the use of only enteral drug administration no effect on infection rates could be demonstrated[59]. The effect of selective decontamination on mortality rate is also still the subject of discussion, either no effect has so far been demonstrated, or the only positive effect is found in subgroups such as patients with trauma[46] or following cardiothoracic surgery[53], or with long-term ICU admission[52] (*Table 7*). Kerver *et al.*[47] have shown an effect on infection-related mortality rate, but the results of Ulrich *et al.*[48] in this regard have been disputed because they 'treated' colonized patients in the test group.

Another important question is whether all patients in the ICU should receive selective decontamination and, if not, which patient groups would benefit from it. Patients after trauma and those with long stays in the ICU may benefit[44,47], as well as patients undergoing major surgical procedures in which the normal anatomy is altered (e.g. oesophageal resection) or in whom defence mechanisms are minimal (e.g. after liver transplantation)[51,60]. The use of selective decontamination in patients who have acute necrotizing pancreatitis is currently under investigation in a national multicentre trial. Adverse effects have been described, but so far these have been minor. Many clinicians have observed the (expected) shift from Gram-negative to Gram-positive micro-organisms (*Staphylococcus epidermidis*, *S. aureus*, enterococci) as causes of infection, but these infections are not difficult to treat[41,46,51,61] McClelland *et al.*[62] described failure of recognition of a perforation peritonitis due to *S. epidermidis* in a patient receiving selective decontamination, the latter preventing culture of 'typical' Gram-negative organisms

The possible emergence of resistance is still under debate. However, no increase in resistance has been reported so far, presumably because the combination of antibiotics in high enteric dosages makes resistance improbable (*Table 7*). The non-absorbable antibiotics suitable for selective decontamination do not reach tissue levels adequate to treat deep organ infection and so they are not in general use; this again minimizes the danger of developing resistance[63].

Conclusion

Selective decontamination is a safe method of reducing Gram-negative colonization and infection in critically ill patients or patients undergoing major elective surgical procedures. It is desirable to start decontamination before operation in those patient groups at risk of developing infection. Selective decontamination alone can lower the rate of wound infection, but is not sufficient to abolish it; decontamination can reduce only endogenous Gram-negative contamination, and influences exogenous contamination only by lowering the number of colonized patients, as a result of which the load of PPMs is reduced. To prevent wound infection, additional measures must be included such as giving systemic perioperative antibiotics or antibiotics suitable for selective decontamination but which also reach efficient tissue levels, such as quinolones[64]

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Anterior resection without a defunctioning colostomy: questions of safety

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The need to defunction the anastomosis at anterior resection remains controversial. As the policy in this unit has been not to perform a defunctioning colostomy during anterior resection, the outcome of a consecutive series of 114 anterior resections, all carried out without a covering colostomy, was studied. During the period February 1985 to September 1991, 21 abdominoperineal resections, six Hartmann's procedures and two resections with coloanal anastomosis were also performed. Within the anterior resection group six clinical leaks (5·3 per cent) occurred, all in the low anastomosis group (8 per cent leak rate) and all of which required an end colostomy. The perioperative mortality rate within the anterior resection group was 3·5 per cent; of the four deaths one was attributable to anastomotic dehiscence and sepsis and the others were due to unassociated medical conditions. The results demonstrate similar leakage and mortality rates to published studies where anterior resection is frequently performed with a defunctioning colostomy. These results indicate that the routine use of a defunctioning colostomy at anterior resection should now be questioned.

In recent years anterior resection has become the operation of choice for lower rectal cancers. Widespread acceptance has been encouraged by the availability of stapling devices which allow anastomosis lower in the pelvis, similar frequency of local recurrence and survival rate to abdominoperineal resection, and patient preference for the avoidance of a stoma[1].

The value of a defunctioning colostomy in patients undergoing low anterior resection remains controversial[2]. Proponents of defunctioning colostomy consider that as it is not possible to predict which anastomoses will leak, and as the consequences of a leak without covering colostomy are more serious, defunctioning colostomy should be performed in all patients. However, only a small proportion of patients with anterior resection develop a clinical leak, and to perform a colostomy in all cases may be unreasonable. Furthermore, with early water-soluble contrast studies, antibiotic usage and nutritional support the consequences of a leak may not necessarily be as serious as previously thought.

In this unit defunctioning colostomy at anterior resection is not performed. Results of the last 114 consecutive anterior resections were studied to determine anastomotic leakage and mortality. It is the contention here that the routine use of a colostomy at anterior resection should be questioned.

Patients and methods

The study included 143 consecutive patients who underwent elective surgery for rectal cancer over the period February 1985 to September 1991. Anterior resection was performed in 114 (79·7 per cent), this was high (tumour completely above the peritoneal reflection) in 40 patients and low (tumour below the peritoneal reflection) in 74. Abdominoperineal resection was performed in 21 patients (14·7 per cent), six patients (4·2 per cent) had a Hartmann's procedure and two (1·4 per cent) had resection and coloanal anastomosis with a covering colostomy. Only patients who presented with a newly diagnosed rectal neoplasm were included in the study.

The 114 patients who underwent anterior resection without defunctioning colostomy form the basis of this report. Seventy patients were male and the mean age was 63·8 (range 36–93) years. Antibiotic prophylaxis was given to all patients; at induction of anaesthesia ceftriaxone 1 g and metronidazole 500 mg were given intravenously, with two further doses of metronidazole administered 8 and 16 h after operation. Anterior resection was performed by standard methods with wide excision of the mesorectum[3]. It was standard policy to mobilize the total left colon and take down the splenic flexure. Preservation of the marginal artery using the mid-colic artery as the main vascular supply was carried out in most patients with anastomosis of the descending colon to the rectal stump. All of the low anterior resection anastomoses were tested with air introduced via the rectum and additional sutures placed if necessary. In 63 patients water-soluble contrast studies were performed 7 days after operation to test anastomotic integrity. Within this group radiological leakage rates were also determined. Clinical leakage was diagnosed when signs of peritonitis were present. Perioperative mortality was defined as death within 1 month of operation.

Results are expressed as mean(s.e.m.) and statistical comparisons are by analysis of variance (ANOVA) or the χ^2 test, as appropriate.

Results

Of the high anterior resections 33 (82 per cent) were sutured by hand, whereas 47 (64 per cent) of the low resections were stapled by the double staple technique (Roticulator 55^+ CEEA; Auto Suture, Ascot, UK). This difference was significant ($\chi^2 = 35{\cdot}4$, $P < 0{\cdot}0001$). *Table 1* shows the age, sex ratio distribution, Dukes' staging and anastomotic type for the two groups.

Table 1 *Age, sex, Dukes' tumour classification and anastomotic type of patients undergoing low and high anterior resection*

	High anastomosis ($n = 40$)	Low anastomosis ($n = 74$)	Total ($n = 114$)
Mean(s.e.m.) age (years)	61·4(2·0)	65·2(1·5)	63·8(1·2)
Sex ratio (M:F)	25:15	45:29	70:44
Villous adenoma*	1 (2)	4 (5)	5 (4·4)
Dukes' classification*			
A	7 (18)	11 (15)	18 (15·8)
B	16 (40)	26 (35)	42 (36·8)
C	12 (30)	22 (30)	34 (29·8)
'D'	4 (10)	11 (15)	15 (13·2)
Anastomosis†			
Sutured	33	27	60
Stapled	7	47	54

*Values in parentheses are percentages. Dukes' 'D' indicates liver metastases. †$P < 0{\cdot}001$ (χ^2 test)

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Table 2 *Details of patients with clinical and radiological anastomotic leakage*

Patient no.	Sex	Age (years)	Dukes' tumour classification	Anastomosis Level	Anastomosis Type	Leak	Outcome
1	M	65	B	Low	Stapled	Clinical	End colostomy
2	M	66	'D'	Low	Stapled	Clinical	End colostomy
3	F	75	B	Low	Sutured	Clinical	End colostomy
4	M	81	B	Low	Stapled	Clinical	End colostomy
5	M	80	A	Low	Stapled	Clinical	End colostomy; died
6	M	82	A	Low	Stapled	Clinical	End colostomy
7	M	63	B	Low	Stapled	Radiological	Pelvic abscess, settled
8	M	77	C	Low	Stapled	Radiological	Settled
9	M	73	C	Low	Sutured	Radiological	Settled

Dukes' 'D' indicates liver metastases

Table 3 *Age, sex, Dukes' tumour classification and anastomotic type of patients showing or not showing leakage*

	Patient group: Leak ($n = 9$)	Patient group: No leak ($n = 105$)
Mean(s.e.m.) age (years)*	73·3(2·4)	63·1(1·4)
Sex ratio (M:F)	8:1	62:43
Villous adenoma†	0 (0)	5 (4·8)
Dukes' classification†		
A	2 (22)	16 (15·2)
B	4 (44)	38 (36·2)
C	2 (22)	32 (30·5)
'D'	1 (11)	14 (13·3)
Anastomosis‡		
High	0	40
Low	9	65
Sutured	2	58
Stapled	7	47
Deaths†	1 (11)	3 (2·9)

†Values in parentheses are percentages. Dukes' 'D' indicates liver metastases. *$P < 0{\cdot}01$ (ANOVA); ‡$P < 0{\cdot}0001$ (χ^2 test)

Clinical anastomotic dehiscence occurred in six patients; all in the low anterior resection group (5·3 per cent of total group or 8 per cent of the low anterior resection group; $\chi^2 = 18{\cdot}62$, $P < 0{\cdot}0001$). All of these patients underwent further laparotomy, the anastomosis was taken down, the rectal stump oversewn and an end colostomy fashioned (*Table 2*). One died from sepsis, the other five were all discharged from hospital healthy; it is not envisaged that their end colostomies will be closed. In the 63 patients in whom water-soluble contrast studies were undertaken three radiological leaks occurred, none of which required any further surgical management (*Table 2*). Seven of the nine anastomotic leaks occurred in a stapled anastomosis (*Table 3*, $\chi^2 = 6{\cdot}15$, $P < 0{\cdot}0001$). After low anterior resection (which included all the patients with leakage), the technique of anastomosis was significantly related to anastomotic leakage (*Table 2*, $\chi^2 = 48{\cdot}4$, $P < 0{\cdot}0001$).

Four deaths occurred (3·5 per cent); one patient in the high anterior resection group died from a brain stem haemorrhage and one from a pulmonary embolus. One patient in the low anterior resection group died from respiratory failure and one died from sepsis following anastomotic leakage. Total leakage rate was not related to Dukes' staging but was significantly related to age (*Table 3*, $P < 0{\cdot}01$). Mortality was also significantly greater with age (mean(s.e.m.) age 78·8(4·3) years for those dying *versus* 64·1(1·2) years for survivors, $P < 0{\cdot}01$).

Discussion

A clinical anastomotic leakage rate of 5·3 per cent occurred in this series of 114 consecutive anterior resections without covering colostomy. All leaks were after low anterior resection, giving a clinical leakage rate of 8 per cent for this procedure. This is in keeping with other reports of clinical leakage rates of between 3 and 19 per cent[4,5]. Certain groups who frequently use a defunctioning colostomy have recently reported lower leakage rates. Karanjia *et al.*[2] report faecal peritonitis in 8 per cent of patients undergoing anterior resection without covering colostomy in contrast to a rate of 0·8 per cent in patients with defunctioning colostomy. In this latter group, however, 16·8 per cent of patients demonstrated radiological evidence of anastomotic leakage, not all of whom remained asymptomatic[2]. Kirwan and colleagues report 3 per cent clinical and 6 per cent radiological anastomotic leakage rates in 100 consecutive anterior resections; 38 per cent of these, however, had a defunctioning colostomy[1]. In addition to the 5·3 per cent clinical leak rate reported in the present study, the results demonstrate radiological evidence of leakage in three of 63 patients (4·8 per cent) tested with water-soluble contrast enemas in the early postoperative period.

The abdominoperineal resection rate during this study was 14·7 per cent, which is low compared with the reported literature and which indicates that a high proportion of patients in this unit are offered sphincter-conserving surgery[1]. Recently, Dixon and colleagues reported a 1 per cent clinical leakage rate for anterior resection; however, their overall anterior resection rate was only 66·6 per cent and included a 24 per cent covering colostomy rate[6]. Karanjia *et al.* report an abdominoperineal resection rate of 9·8 per cent over a 10-year period, which is the lowest yet reported, although it is unclear whether this is in a consecutive series of patients presenting with rectal cancer[2].

Many still consider a colostomy necessary during low anterior resection, although its use appears to be declining It is presumed that a covering colostomy lessens the consequences of anastomotic dehiscence, but whether this is true is not clear[7]. Peritoneal soiling and peritonitis, while rare, can still occur in the presence of a colostomy[2]. Furthermore, early detection of leakage by water-soluble contrast enema in patients with clinical suspicion of leakage may limit its consequences by the institution of appropriate antibiotic therapy, nutritional support and prompt surgery if indicated. With these measures overall morbidity and mortality rates may not be unduly high as demonstrated in this and other studies[5,8]. In this series only one death occurred as a consequence of anastomotic dehiscence and the overall mortality rate was 3·5 per cent.

Despite the usefulness of routine water-soluble contrast enemas in detecting radiological leakage and allowing appropriate supportive treatment, this investigation is not without risk. The authors feel confident in attributing one of the six clinical leaks reported here to the injudicious performance of a water-soluble contrast enema 6 days after surgery. In the light of this experience the policy of routine contrast enemas has been reviewed and its use is now reserved for patients in whom a suspicion of leakage has arisen

All leaks in this study occurred in the low anterior resection group. The definition of low and high resection used here is based on the anatomical markings of the peritoneal reflection which extend to between 5·5 and 7·5 cm from the anal verge, depending on sex[9]. Tumour height has not been based on digital or sigmoidoscopic distance from the anal margin as we believe that this can be misleading because of alteration in position of the tumour and/or rectum following rectal mobilization. This definition has also been used by Turnbull *et al* to identify those anastomoses at high risk of dehiscence[10] and it correctly predicted the high-risk group of patients who developed anastomotic dehiscence in this series.

Anastomotic dehiscence in the stapled group was significantly greater than in the sutured group. This is not unexpected, as with the ease of use of these devices low in the pelvis there was a predominance of stapled anastomoses in the low anterior resection group. Other prospective studies have demonstrated no difference in leakage rates between sutured and stapled anastomoses in low anterior resection[11,12]

The avoidance of colostomy results from many influences, including patient preference The disability arising from a colostomy is important in the elderly and may limit independence. Furthermore, in certain cases the stoma may not be closed, and closure itself can lead to significant morbidity and (rarely) mortality[2,13,14]. Total hospital stay is also prolonged with the addition of a stoma[7]. This and the continuing need for stoma appliances contribute to the total economic cost of the colostomy. High anterior resection can be performed safely without colostomy. We believe that it is unreasonable to subject all patients undergoing low anterior resection to a covering colostomy as at present it appears impossible to predict those anastomoses at risk of leakage accurately[15]. As anastomotic leakage and mortality rates in this series are comparable to those of other reported series where a covering colostomy is frequently used, we feel that the routine use of a colostomy at low anterior resection should now be questioned.

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Poor palliation of colorectal malignancy with the neodymium yttrium–aluminium–garnet laser

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The neodymium yttrium–aluminium–garnet (NdYAG) laser was used to palliate the symptoms of 38 patients with rectal carcinoma unsuitable for radical surgery. All patients with small tumours ($n = 6$) *reported resolution of their symptoms. In contrast, those with large tumours frequently showed little improvement* ($n = 18$) *and alternative surgical management was necessary in 12 patients. The overall early mortality rate (<1 month after first treatment) was 21 per cent. The NdYAG laser offers good palliation and may even cure small colorectal tumours in patients who are unsuitable for surgery. For large circumferential tumours, those associated with obstruction and those close to or involving the anal sphincters, however, the results are poor and better symptom control may be achieved by other means.*

Recent reports have suggested that the neodymium yttrium–aluminium–garnet (NdYAG) laser can offer good long-term palliation to those patients with colorectal malignancy considered unfit for surgery[1–4]. Such palliation should relieve obstruction and control the symptoms of bleeding, tenesmus and mucus discharge as quickly as possible and with minimum discomfort to the patient.

This study was designed to determine whether such optimism is confirmed and to determine which patients derive most benefit from this treatment.

Patients and methods

Thirty-eight consecutive patients with colorectal malignancy proven by biopsy were studied and followed up to death or for a minimum of 18 months There were 19 men and 19 women aged 52–93 (mean 75) years Primary malignancy occurred in 26 patients and 12 had recurrent tumour. Ten patients refused surgery and 12 were considered unfit for operation because of coexisting medical problems, including severe cardiac failure and chronic obstructive airway disease. In 16 patients, including the 12 with recurrent tumour, involvement of other pelvic structures or metastases meant that the disease was inoperable

All tumours were graded, at the time of initial assessment, for the degree of luminal obstruction (1, endoscope passes with ease, 2, endoscope passes with difficulty; 3, endoscope would not pass but a lumen is visible, 4, no visible lumen), length and the percentage of bowel circumference involved This enabled the tumours to be grouped into small (lumen grade 1, <5 cm long, <25 per cent circumference involved) and large (grades 2–4, ⩾5 cm long, ⩾25 per cent circumference involved). The distance of the lower margin from the anal verge for all tumours is shown in *Table 1*. Most tumours were situated in the rectum, but seven were >15 cm from the anal margin

All treatments were performed under sedation with intravenous diazepam. Between 2000 and 10 000 J per session were administered using a NdYAG laser Initially, treatment was repeated until a good lumen was achieved and then, where necessary, was given monthly All patients were followed up regularly.

Treatment was considered successful if the patient's symptoms of obstruction, tenesmus, bleeding and mucus discharge improved so that they could return home and remain free of symptoms.

Results

The results are summarized in *Table 2*.

All six patients with small tumours did well with good control of their symptoms Two patients died from other causes (myocardial infarction and coexisting carcinoma of the bronchus) before an accurate assessment could be made. Of the four cases that were assessable, three had no evidence of disease on biopsy and one had residual disease but no symptoms.

The 32 patients with large tumours (⩾5 cm long, ⩾25 per cent circumference involved) included all those with recurrent tumour. The survival rate in this group was poor. Sixteen died within 3 months of referral and only four survived for >6 (mean 4) months. The median lumen grade was 4 with a range of 1–4. All have undergone one to 13 (median three) treatments. The total energy given during treatment varied from 2341 to 96 349 (mean 24 760) J. Only 25 of these patients could be assessed: six died within 1 month of treatment and one patient had a large cavitating lesion that was unsuitable for laser therapy. Eleven patients have been referred for surgery: the major indication was colonic obstruction, present at the time of referral and not relieved with the laser (five patients), or developing during treatment (two patients). Colostomy was performed in two patients for persistent diarrhoea and in two for relief of rectovaginal fistula. Three patients showed no improvement in symptoms and continued passing eight to 12 mucus bowel actions per day. One patient was made worse by treatment and a further two showed initial improvement but relapsed during treatment Eight patients have shown sustained improvement with a reduction in bleeding and in the number of bowel motions; the tumours in six of these patients were >10 cm from the anus and in the remaining two were 5–10 cm from the anal verge

Table 1 *Site of tumours treated with NdYAG laser*

Distance of lower margin from anal verge (cm)	No. of small tumours	No. of large tumours
<5	1	5
5–10	0	11
11–15	2	12
16–20	3	2
>20	0	2

Table 2 *Outcome of laser treatment in 38 patients*

	No of small tumours ($n = 6$)	No of large tumours ($n = 32$)
Complete resolution	3	0
Residual disease, symptoms controlled	1	8
No improvement, symptomatic treatment	0	6
No improvement, surgery	0	11
Unassessable	2	6
Unsuitable for laser treatment	0	1

Based on a presentation given to the British Society of Gastroenterology, April 1990 and published in abstract form as Gut *1990, 31 A604*

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Discussion

The results achieved for small tumours in this series agree with those reported by other workers[1,2]. While many of these tumours may be amenable to treatment by other, less costly means, particularly when they occur below the peritoneal reflection, the NdYAG laser offers an alternative to colonoscopic diathermy and open operation for more proximal tumours.

For large carcinomas the results presented here are worse than those reported by others, who describe a favourable symptomatic outcome in up to 75 per cent of cases and survival up to 24 months[1,2] This would appear to contradict an earlier report in which we described early functional improvement[3]. This discrepancy is due to the larger number of patients referred with colonic obstruction and failure to maintain continence in patients with luminal patency. We feel that two factors contribute to loss of continence: involvement of the sphincters with tumour and loss of rectal compliance secondary to involvement by tumour and fibrosis. As 50 per cent of these patients had tumours within 10 cm of the anus, and 87 per cent had tumours within 15 cm, the poor functional results for large tumours reported here are not surprising

Circumferential involvement and the presence of complete or partial colonic obstruction are both said to be associated with a poor response to laser therapy, although some authors have advocated laser therapy as a means of recanalizing the colon before resection[4,5]. Three-quarters of the patients with large tumours in this series had >75 per cent circumferential involvement and five were referred with colonic obstruction.

The patients in this study were extremely frail, as demonstrated by their poor overall survival rate. Indeed, eight died before an accurate assessment of response could be made. The poor survival of these patients suggests that they had more advanced disease than those in some other series[1,2,4,6,7] Indeed, it could be argued that some of the patients in this study should not have been treated at all, as the benefit provided during their last few weeks of life was minimal.

The NdYAG laser provides an alternative to open surgery in unfit patients and is particularly valuable for treating smaller, non-obstructing tumours in the colon and upper rectum. Larger tumours and those in the lower rectum are better palliated by other surgical techniques A defunctioning colostomy can safely be performed under local anaesthesia and often gives significant relief of symptoms, particularly when they are related to obstruction. Consideration should also be given to local excision, diathermy or transanal endoscopic resection, but these are not suitable for lesions above the peritoneal reflection.

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Announcement

International Hepato-Biliary-Pancreatic Association Frank Glenn Travelling Fellowship 1992

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Applications should be sent to Dr Haile T. Debas, University of California, San Francisco, Department of Surgery, San Francisco, CA 94143-0104, USA by 30 April 1992. Telephone: (415) 476-1236. Facsimile· (415) 476-1734.

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Experimental study of the protective effect of intermittent hepatic pedicle clamping in the rat

The tolerance of the liver to ischaemia during intermittent clamping of the hepatic pedicle was compared with that during a continuous Pringle manoeuvre. Three groups of rats undergoing total durations of clamping of 60, 90 and 120 min were studied. A temporary peroperative portacaval shunt was used to exclude the effects of splanchnic venous stasis and allow independent study of the effects of hepatic ischaemia. In each group, three methods of portal clamping were evaluated: a continuous Pringle manoeuvre (n = *10*)*, a 30-min intermittent clamping* (n = *10*) *and a 15-min intermittent clamping* (n = *10*)*. The clamp release time between the periods of liver ischaemia was 5 min. Survival at day 7 and postoperative changes in liver function* (*transaminase enzymes, bilirubin, bromsulphthalein elimination, liver adenosine 5′-triphosphate levels*) *were recorded. Intermittent clamping of the pedicle was tolerated significantly better than continuous clamping. This method optimizes the ability of the liver to tolerate extended periods of ischaemia. For a given duration of ischaemia, no additional improvement could be produced by shortening the intermittent clamping period from 30 to 15 min. These data suggest that, when the Pringle manoeuvre is used, it should be applied intermittently rather than continuously.*

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Intraoperative bleeding is known to be an important prognostic indicator of both morbidity and mortality following liver resection. Temporary clamping of the hepatic pedicle, as described by Pringle[1], is one of the methods used to limit haemorrhage from the plane of resection. However, this benefit is counterbalanced by adverse effects of the interruption of hepatic inflow, particularly liver ischaemia and splanchnic venous stasis. In animals, these two factors were thought to be responsible for the poor tolerance of most species to the Pringle manoeuvre. However, MacKenzie *et al.*[2,3] subsequently demonstrated in the dog that the invariable death of the animals after 30 min of clamping was, in fact, due mainly to splanchnic venous stasis. Indeed, ischaemia of 60 min without splanchnic stasis was well tolerated in 83 per cent of animals[2,3].

In humans, Huguet *et al.*[4] challenged the classical concept that 15–20 min of clamping was the maximum safe time of hepatic inflow occlusion and it is now widely accepted that the healthy human liver can tolerate an ischaemic period of up to 60 min in normothermia[5]. Nevertheless, hepatic surgeons are often reluctant to perform a prolonged Pringle manoeuvre because the degree of liver injury, as reflected by postoperative increases in transaminase levels, has been reported to be related directly to the duration of ischaemia, after either hepatic inflow occlusion in animals[6] or total vascular exclusion in humans[5]. Moreover, the relative importance of ischaemia and splanchnic venous stasis after prolonged clamping in humans is poorly understood.

In order to minimize the consequences of ischaemia on the liver, a method of repeated intermittent clamping followed by a short period of reperfusion, rather than continuous clamping, has been studied in cases of prolonged pedicle occlusion. This procedure was used by Makuuchi *et al.*[7] during hemihepatic vascular occlusion, but its benefits over a continuous Pringle manoeuvre during total hepatic inflow occlusion remain to be determined. Therefore, an experimental study has been conducted in the rat to determine the safest method of liver inflow occlusion, comparing repeated intermittent clamping of the hepatic pedicle with continuous clamping, performed for identical total periods of ischaemia.

Materials and methods

Male Sprague–Dawley rats, weighing 250–270 g and fed with standard biscuits, were used

In view of the poor tolerance of animals to prolonged splanchnic vascular occlusion, all experiments included a temporary portacaval shunt to prevent splanchnic congestion and allow independent study of the effect of hepatic ischaemia during occlusion of the hepatic pedicle.

Operative procedure

The abdomen was opened through a midline incision under ether anaesthesia. After dissection of the portal vein, the hepatic artery and the bile duct, a side-to-side anastomosis between the portal vein and the inferior vena cava was performed using 8/0 silk. The time required to perform this anastomosis was approximately 8 min. The portal vein, hepatic artery and bile duct were then clamped simultaneously between the shunt and the liver When intermittent ischaemia was performed and the clamp released, the anastomosis was temporarily closed by gently pulling the suture around the anastomosis so that all of the portal blood flowed into the liver (*Figure 1*). After 5 min, the clamp was replaced on the hepatic pedicle, and the suture around the anastomosis was loosened, so that portal vein blood again flowed into the inferior vena cava At the conclusion of the period of ischaemia, the anastomosis was ligated, care being taken not to constrict the portal vein (*Figure 1*)

Animals were allocated at random into three experimental groups with a total duration of ischaemia of 60 (n = 10), 90 (n = 10) or 120 (n = 10) min. When performing intermittent ischaemia, clamping was performed for 15-min or 30-min periods with 5 min of reperfusion between each period, repeated until a total of 60, 90 or 120 min of ischaemia had been attained

When the entire period of ischaemia had been completed, a sample of liver tissue was removed, 5 min after the clamp was released, in order to measure liver tissue adenosine 5′-triphosphate (ATP) levels The sample was preserved in liquid nitrogen After completion of the surgical procedure and closing the abdomen, animals were allowed to resume normal eating and drinking.

Assessment of tolerance to liver ischaemia

Survival rate Animals were considered to have survived the procedure if they remained alive on the seventh day after operation

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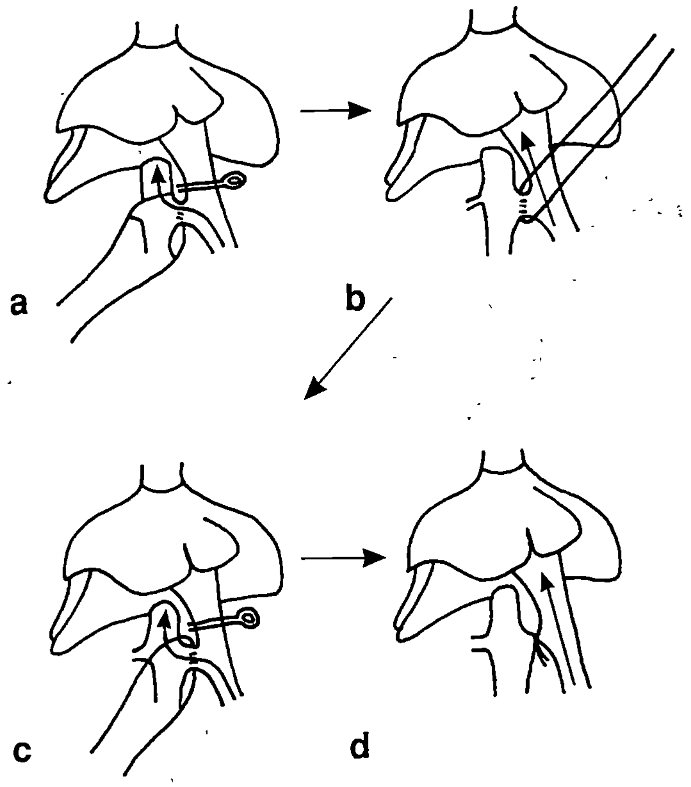

Figure 1 *Technique for hepatic pedicle clamping.* **a**; **c** *During clamping, the portacaval shunt diverts splanchnic blood to the vena cava. When the clamp is released, the shunt can be closed to restore normal portal inflow, by* **b** *pulling on the suture or* **d** *ligating the shunt at the end of the procedure*

Liver function tests. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), alkaline phosphatase and total bilirubin levels were determined before operation and 1, 3, 5, 7 and 15 days after operation using routine methods (SGOT, SGPT, alkaline phosphatase: Biotrol, Paris, France; LDH, total bilirubin: Diagnostica; Boehringer Mannheim, Paris, France)

The bromsulphthalein elimination rate was also determined before operation and 1, 3, 5, 7 and 15 days after operation by intravenous administration of bromsulphthalein 5 mg/100 g into the penile vein, with collection of samples 2, 3, 5 and 6 min later, and calculation of the elimination rate (K value).

Assessment of liver energy levels following ischaemia Approximately 500 mg liver tissue was removed 5 min after the final release of the clamp. ATP levels were measured using the method of Jaworec *et al.*[8].

Statistical analysis. The χ^2 test (or modified χ^2 test) was used for comparison of survival rates, and analysis of variance (ANOVA) for comparison of the results of liver function tests.

Results

Survival

Survival rates on the seventh day after operation are shown in *Table 1*. After 60-min ischaemia, the survival rate in the continuous ischaemia group was 80 per cent (eight of ten rats); it was 90 per cent (nine of ten) in both the 30-min and 15-min intermittent ischaemia groups. As the duration of ischaemia was extended to 90 and 120 min, the survival rate in the continuous ischaemia group fell to 40 per cent (four of ten) and 20 per cent (two of ten), respectively, whereas survival in both the 30-min and 15-min intermittent ischaemia groups was maintained at 80 per cent (eight of ten) and 70 per cent (seven of ten), respectively. At 120 min the difference between the continuous group and the cumulated intermittent groups was significant ($P < 0{\cdot}05$).

Postoperative liver function tests

Serum glutamic oxaloacetic transaminase. A peak was observed in all the animals on day 1, after which the SGOT levels returned to normal from day 3. When SGOT levels at day 1 were examined, there was no difference between the continuous ischaemia group and both the 15-min and 30-min intermittent ischaemia groups at a total ischaemic time of 60 min (*Figure 2*). When the duration of ischaemia was extended to 90 and 120 min, however, the continuous ischaemia group had markedly increased levels compared with both the 30-min and 15-min intermittent groups (*Figures 3* and *4*). The difference between the continuous ischaemia group and each of the intermittent ischaemia groups was significant at 90 and 120 min, respectively ($P < 0{\cdot}05$ and $P < 0{\cdot}01$).

Serum glutamic pyruvic transaminase. Similar results to those for SGOT were observed for SGPT.

Lactic dehydrogenase. LDH levels remained almost entirely within the normal range from day 1 after operation in the surviving animals, with no subsequent elevations. However, in animals that died mean(s.d.) LDH levels on the first day after operation were significantly higher (23 468(30 557) units/l) than those of survivors (711(562) units/l) ($P < 0{\cdot}01$).

Total bilirubin. There was no significant difference in postoperative serum bilirubin levels between groups, in terms of the duration (60, 90 or 120 min) or method (intermittent or continuous) of clamping.

Alkaline phosphatase. Alkaline phosphatase values were almost always within the normal range after surgery, and no significant differences were detected with respect to either the duration or method of ischaemia.

Bromsulphthalein Mean postoperative bromsulphthalein K values for all rats were lowest on the first day after operation,

Table 1 *Survival at 7 days after continuous and intermittent hepatic pedicle clamping for 60, 90 and 120 min*

Duration (min)	Continuous clamping	Intermittent clamping	
		(n × 30 min)	(n × 15 min)
60	8 of 10	9 of 10	9 of 10
90	4 of 10	8 of 10	7 of 10
120	2 of 10*	8 of 10*	7 of 10*

*$P < 0{\cdot}05$ (continuous *versus* cumulated intermittent groups, χ^2 test)

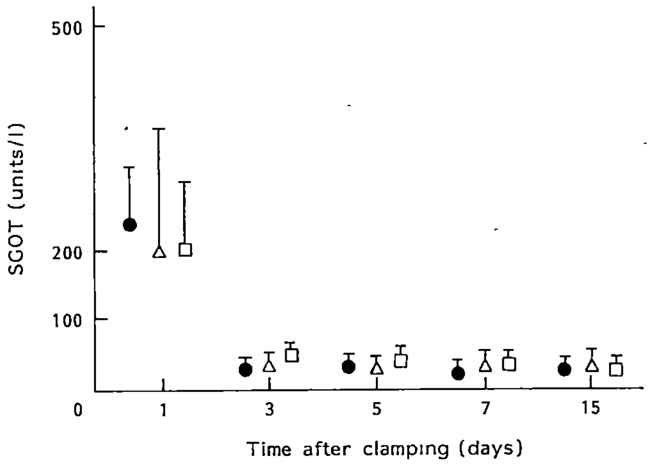

Figure 2 *Mean(s.d.) serum glutamic oxaloacetic transaminase (SGOT) levels after clamping of the hepatic pedicle for 60 min using continuous* (●), *30-min intermittent* (△) *and 15-min intermittent* (□) *occlusion (normal value 24·8(6·3) units/l). There were no significant differences between the groups (ANOVA)*

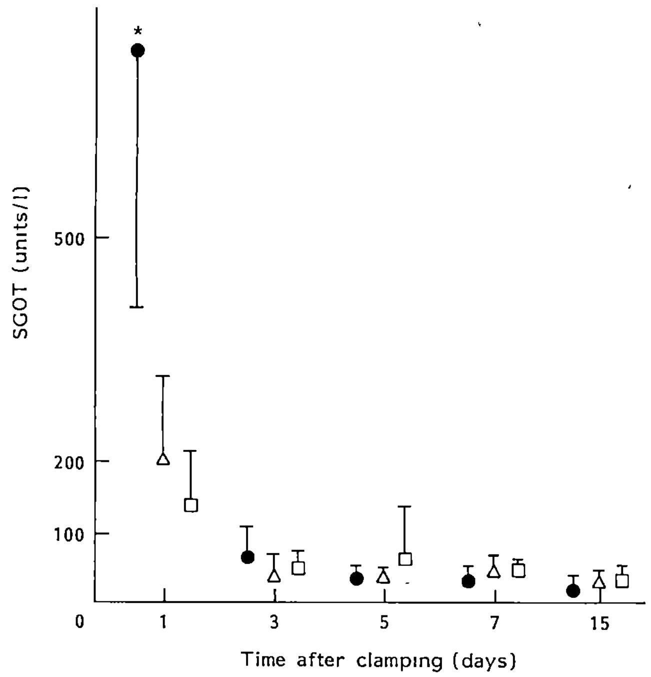

Figure 3 *Mean(s.d.) serum glutamic oxaloacetic transaminase (SGOT) levels after clamping of the hepatic pedicle for 90 min using continuous* (●), *30-min intermittent* (△) *and 15-min intermittent* (□) *occlusion.* $^{*}P < 0{\cdot}05$ (*continuous* versus *each intermittent group, ANOVA*)

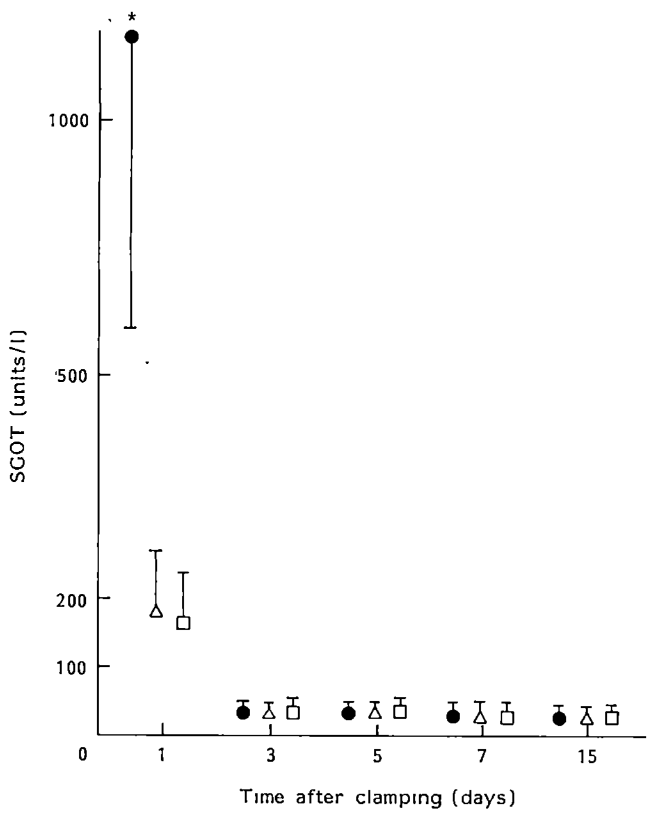

Figure 4 *Mean(s.d.) serum glutamic oxaloacetic transaminase (SGOT) levels after clamping of the hepatic pedicle for 120 min using continuous* (●), *30-min intermittent* (△) *and 15-min intermittent* (□) *occlusion* $^{*}P < 0{\cdot}01$ (*continuous* versus *each intermittent group, ANOVA*)

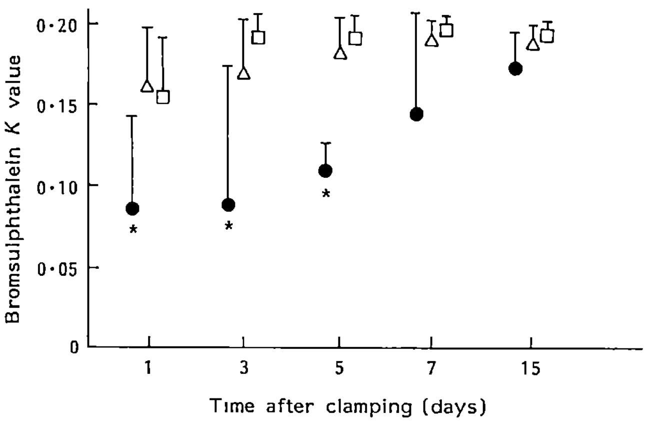

Figure 5 *Mean(s.d.) bromsulphthalein* K *values for animals undergoing a total of 120-min clamping using continuous* (●), *30-min intermittent* (△) *and 15-min intermittent* (□) *occlusion* $^{*}P < 0{\cdot}01$ (*continuous* versus *each intermittent group, ANOVA*)

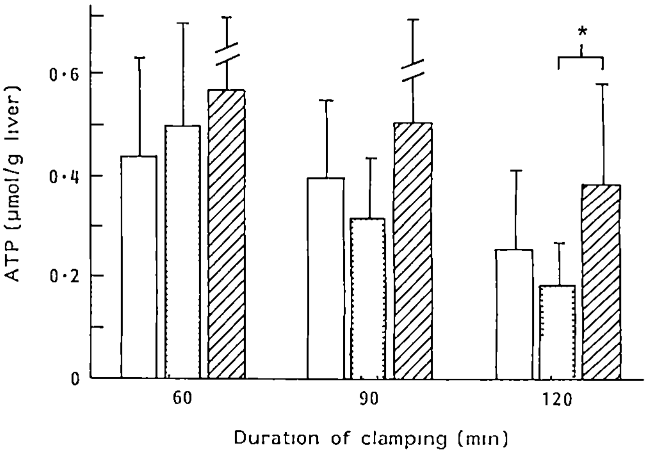

Figure 6 *Adenosine 5'-triphosphate (ATP) levels in the continuous* (□), *30-min intermittent* (▤) *and 15-min intermittent* (▨) *groups following 60, 90 and 120 min clamping of the hepatic pedicle.* $^{*}P < 0{\cdot}05$ (*15-min intermittent* versus *30-min intermittent group, ANOVA*)

then gradually recovered, returning almost entirely to within the normal range by day 15. No significant differences were found between the groups in terms of either duration or method of ischaemia up to 90 min of total ischaemia. After 120 min, however, the continuous ischaemia group had lower K values than the intermittent ischaemia groups (*Figure 5*). This difference was significant on days 1, 3 and 5 ($P < 0{\cdot}01$).

Liver tissue energy (ATP levels 5 min after ischaemia)

When ATP concentrations were measured, lower levels were demonstrated in the continuous ischaemia group than in the 15-min intermittent ischaemia group, but the difference was not statistically significant. At 120 min, ATP levels were significantly higher in the 15-min intermittent group than in the 30-min intermittent group ($P < 0{\cdot}05$) (*Figure 6*).

Discussion

As perioperative haemorrhage is reported to be associated with increased morbidity and mortality rates after liver resection[9,10] and a decreased time to recurrence in cases of malignant disease[11], any technique for reducing bleeding is valuable to the hepatic surgeon. Clamping of the hepatic pedicle is one of the simplest and most commonly used methods.

The purpose of this study was to determine whether an intermittent or continuous Pringle manoeuvre is safer for prolonged periods of liver ischaemia in the rat. In contrast to the situation in humans, rats are known to be highly sensitive to splanchnic stasis and a 50 per cent mortality rate has been reported[12] when the portal vein is occluded for just 30 min. Hence, the experimental model in the rat must include a procedure that avoids splanchnic venous stasis, so permitting the effects of liver ischaemia to be studied in isolation Procedures such as extracorporeal shunts[13,14] or partial portal clamping, followed by resection of the non-ischaemic liver[15], have been described, but these techniques are imperfect because of the difficulty of ensuring shunt patency in the former, and the need for hepatectomy of the non-ischaemic liver in the latter. Consequently, a technique was developed of a direct side-to-side portacaval shunt (encircled by a silk suture), which produces a complete decompression of the splanchnic venous bed that can be simply reversed.

When the results of the two methods of the Pringle manoeuvre were compared, the superiority of intermittent clamping over the continuous method was clearly demonstrated. The survival rate decreased with longer periods of ischaemia in the continuous group (80, 40 and 20 per cent respectively after 60, 90 and 120 min), but was maintained (70–80 per cent) in the intermittent groups, even when the total period of ischaemia was increased to 90 and 120 min Death of the animals was presumably related to the consequences of liver ischaemia, as splanchnic venous stasis was prevented by the portacaval shunt. Thus, intermittent clamping appeared to be an effective method of minimizing the deleterious effect of ischaemia. This finding was supported by the markedly lower serum levels of transaminases (SGOT and SGPT) observed in both intermittent groups compared with the continuous group at 90 and 120 min of ischaemia.

A similar improvement in liver tolerance, as indicated by bromsulphthalein clearance, was found in the intermittent compared with the continuous vascular occlusion group at 120 min of ischaemia. Similarly, postischaemic liver tissue ATP levels were higher in the 15-min intermittent group compared with the continuous or 30-min intermittent ischaemia groups.

An interesting finding in the postoperative course after ischaemia was that no additional benefit, except for ATP levels at 120 min, was observed by increasing the number of clamping–release episodes or by shortening the ischaemic period from 30 to 15 min, as measured by rate of survival, increase of transaminase or bromsulphthalein *K* values.

In summary, the intermittent clamping technique is an efficient procedure for limiting liver failure caused by prolonged liver ischaemia This beneficial effect was demonstrated in this model to result from a reduction in the liver injury caused by ischaemia alone. Thus, in addition to the recent attempts at pharmacological prevention of postischaemic hepatic dysfunction with agents such as chlorpromazine, prostacyclin and oxygen free radical scavengers[16], intermittent clamping provides a technical means of improving the tolerance of the liver to a prolonged period of ischaemia However, no additional improvement was obtained in this study by shortening the periods of occlusion from 30 to 15 min.

In clinical practice, an intermittent rather than a continuous clamping of the hepatic pedicle is likely to increase the ability of the liver to tolerate the consequences of prolonged ischaemia and splanchnic venous stasis[10]. The ideal length of time for which the hepatic pedicle should be intermittently clamped remains to be determined in humans. This experimental study presents a rat model suitable for exploring different methods of pedicle clamping, and suggests that the intermittent method has considerable benefits

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Audit of open cholecystectomy in a district general hospital

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This retrospective study audited all non-malignant biliary surgery carried out in a district general hospital between January 1985 and December 1990. Surgery was performed on 722 patients: 555 (77 per cent) were women and 167 (23 per cent) were men. The mean(s.d.) age of the patients was 49(16) years. Elective admissions accounted for 70 per cent of cases and 30 per cent were emergency admissions. Ultrasonography confirmed the diagnosis in 93 per cent of cases. An elective operation was performed in 542 patients and 180 patients underwent an urgent or emergency operation. Simple cholecystectomy was performed on 616 patients (85 per cent); 92 (13 per cent) also underwent common bile duct exploration and 14 (2 per cent) had an additional unrelated procedure. The mean(s.d.) hospital stay was 12·3(6·3) (range 4–34) days. There was one perioperative death. The general overall morbidity rate was 25 per cent and the procedure-related morbidity rate was 7 per cent. For simple cholecystectomy (n = 630) there were no deaths; the general morbidity rate was 15 per cent and the procedure-related rate was 3 per cent.

New techniques in the management of gallstone disease must meet very exacting criteria to compare with open cholecystectomy, which remains the standard procedure[1]. The results must compare mortality, morbidity and outcome rates. No data are available to make comparisons between laparoscopic and conventional procedures. Reduced hospital stay, short recovery periods, cost factors and cosmetic advantages of laparoscopic techniques may not be sufficient reason to permit unfettered use. A critical audit of current results achieved with open cholecystectomy seems pertinent to define the optimum treatment for gallstone disease.

Patients and methods

A retrospective review of all biliary surgery performed by a two-surgeon unit was carried out for the period from January 1985 to December 1990 There were 732 consecutive biliary operations performed for non-malignant disease Information was incomplete or unavailable in ten patients (1 per cent), each of whom had a simple cholecystectomy with no serious complications Nineteen symptomatic patients settled on conservative therapy and were considered unfit or inappropriate for open surgery. Information was obtained from the department's internal audit, theatre records, patients' charts and the hospital's internal activity analysis. Records were cross-referenced to ensure accuracy. The study analysed the presentation, investigation, treatment, pathology, hospital course and outcome.

Most patients received preoperative single-dose prophylactic antibiotics. There was no consistent postoperative antibiotic policy In the first 2 years of the study only half of the patients received subcutaneous heparin prophylaxis. In the latter part the vast majority were receiving heparin All patients underwent general anaesthesia A unilateral intercostal block was administered to 180 patients, 85 had bilateral intercostal blocks and three received epidural analgesia Peritoneal drains were used selectively only during the first 2 years of the review Elective operations were those performed in planned admissions; urgent operations were those performed within 5 days of an acute admission, and emergency operations were those within 24 h of an acute admission.

Perioperative death was defined as that occurring within 30 days of surgery. The minimum follow-up for recording complications extended to the first postoperative visit, which ranged from 4 to 6 weeks after surgery Complications after this period were recorded during subsequent outpatient visits or through notification by general practitioners. Late morbid events may not have been recorded

Results

Of the 722 patients analysed 555 (77 per cent) were women and 167 (23 per cent) were men. The mean(s.d.) age was 49(16) years and 25 per cent were over 65 years old (*Figure 1*). There were 221 patients (31 per cent) who presented with acute symptoms. The range of presenting symptoms is shown in *Table 1*. The mean(s.d.) time interval between diagnosis and operation was 3·4(11·4) weeks. Thirteen patients underwent emergency cholecystectomy, 167 had an urgent cholecystectomy and 542 patients underwent elective procedures. The majority of patients admitted to hospital with acute symptoms underwent surgery during that same hospital admission. A consultant surgeon performed 506 (70 per cent) of the operations and 216 (30 per cent) were performed by a registrar. There were 616 cholecystectomies (85 per cent) and 92 cholecystectomies with common bile duct (CBD) exploration (13 per cent), of which 83 had a supraduodenal and nine a transduodenal exploration. A second unrelated procedure was performed in 14 patients (2 per cent).

Simple cholecystectomy lasted for a mean(s.d.) of 85(25) min and that with CBD intervention 132(36) min

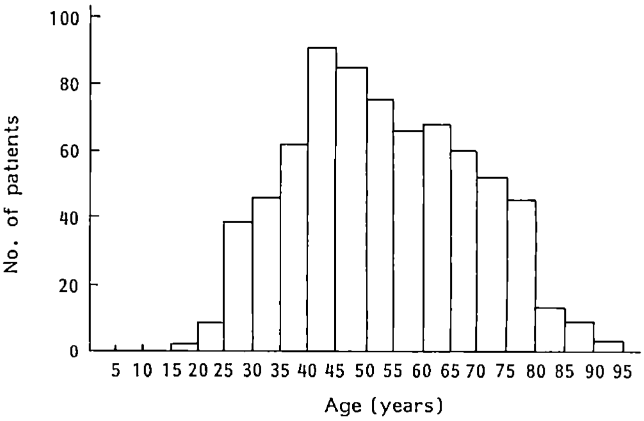

Figure 1 *Age distribution of the 722 patients presenting to surgery*

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Table 1 *Presenting symptoms in 722 patients*

Symptom	*n*
Upper gastrointestinal dyspepsia	273
Gallbladder/biliary colic	169
Acute cholecystitis	163
Non-specific symptoms	51
Obstructive jaundice	50
Gallstone pancreatitis	11
Acute cholangitis	5

Table 2 *Operative and pathological findings*

Finding	*n*
Operative (*n* = 722)	
Chronically inflamed gallbladder	364
Acutely inflamed gallbladder	179
Normal-looking gallbladder	77
Distended oedematous gallbladder	76
Mucocele	13
Gangrenous gallbladder	26*
Pathology (*n* = 722)	
Chronic cholecystitis	495
Acute cholecystitis	149
Hypertrophied gallbladder	50
Normal gallbladder	13
Gangrenous gallbladder	13
Gallbladder adenoma	2

*Three of these patients had a perforated gallbladder and biliary peritonitis

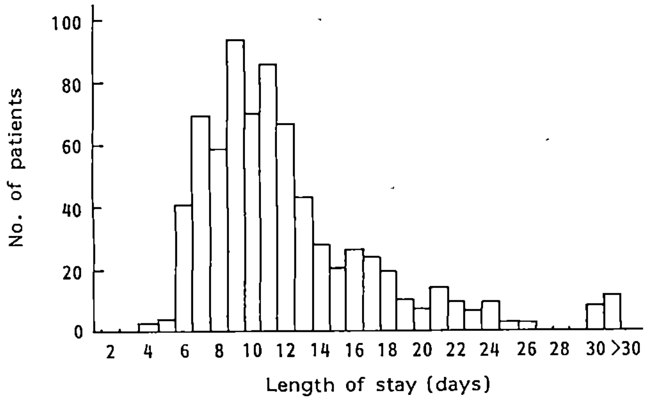

Figure 2 *Distribution of the overall length of hospital stay for the 722 patients*

Table 3 *General complications*

Complication	Cholecystectomy only (*n* = 630)	Cholecystectomy and CBD exploration (*n* = 92)
Lower respiratory tract infection	38	29
Atelectasis	34	16
Urinary tract infection	6	6
Urinary retention	10	0
Cardiac arrhythmia	2	4
Left ventricular failure	3	2
Septicaemia	0	5
Angina	2	2
Pulmonary embolus (non-fatal)	1	2
Miscellaneous	1	2
Total	97	68

CBD, common bile duct

Table 4 *Procedure-related complications*

Complication	Cholecystectomy only (*n* = 630)	Cholecystectomy and CBD exploration (*n* = 92)
Wound infection	12	9
Retained stones	0	8
Subphrenic collection	2	4
Paralytic ileus	1	3
Pancreatitis	0	2
Biliary leak	0	2
Perioperative small bowel perforation	0	1
T tube-related cholangitis	0	1
Pneumothorax (intercostal block)	2	0
Total	17	30

CBD, common bile duct

Routine peroperative cholangiography was performed in 665 patients (92 per cent). There were 573 normal (79 per cent) and 92 abnormal (13 per cent) cholangiograms. In 57 patients (8 per cent) cholangiography was not performed. No stones were found in two of the CBD explorations at surgery or during follow-up (a false positive rate of 2 per cent). The macroscopic appearance of the gallbladder at surgery and the subsequent histopathological findings are shown in *Table 2*.

The mean(s.d.) length of hospital stay was 12·3(6·3) (range 4–34) days (*Figure 2*). The mean(s.d.) preoperative stay was 2·5(2·8) days; most elective patients were admitted the day before surgery. The mean(s.d.) overall postoperative stay was 9·8(6·4) days. The postoperative stay for simple cholecystectomy was 7·7(4·2) days. There was one perioperative death. This occurred in a 73-year-old man with a 4-week history of acute relapsing pancreatitis with cholelithiasis and choledocholithiasis who underwent cholecystectomy, CBD decompression, and pancreatic bed debridement and drainage. He died 4 days after surgery. There were 212 complications in 177 patients, giving a general overall morbidity rate of 25 per cent and a procedure-related morbidity rate of 7 per cent. For simple cholecystectomy there were 114 complications in 95 patients, giving a general morbidity rate of 15 per cent and a procedure-related morbidity rate of 3 per cent. The number and nature of the complications are shown in *Tables 3* and *4*. The major procedure-related complications included eight patients with retained CBD stones who required six endoscopic and two T tube stone extractions. There were six subphrenic biliary collections of which three required ultrasonographically guided drainage. Three resolved without intervention.

Discussion

The present study confirms that simple cholecystectomy can be performed in non-specialist centres with no mortality. This outcome can be achieved in patients with acute cholecystitis undergoing urgent or early cholecystectomy[2–4]. The proportion of patients in this series with a mucocele or gangrene of the gallbladder was similar to that reported by others[2], but only three patients had biliary peritonitis secondary to a perforated gallbladder. This condition is associated with a significant mortality rate[5].

No bile duct injuries occurred. Most of the reported duct injuries occur in operations where peroperative cholangiography is omitted[6,7]. Peroperative cholangiography should be routinely performed in all cases. In this series 13 per cent of CBDs were explored, and all but two patients had stones. The one death was in a patient who might have been more appropriately managed by earlier intervention. A disappointing aspect of this audit is the 9 per cent rate of stone retention which is much higher than is now considered acceptable[8–10]. Choledochoscopy was not performed and may account for this high rate. The higher general and procedure-related morbidity rates for cholecystectomy with CBD exploration were related mostly to cardiorespiratory complications and procedure-related sepsis. There is a higher incidence of wound sepsis after emergency or urgent surgery and in elective operations after choledochotomy is performed[11]. The procedure-related sepsis rates compare favourably with those from other series[1,11–16]. There were only three pulmonary emboli documented and no deep vein thrombosis recorded.

The criteria of safety and efficacy are the measures of any surgical operation. Open cholecystectomy satisfies these criteria[1,12,16]. Early reports suggest that similar results can be achieved with laparoscopic cholecystectomy in specialist centres[17]. Some concern has been expressed about procedure-related morbidity, particularly bile duct injuries[18,19]. The suggestion that most of this morbidity is related to a learning curve is not found in many other interventional endoscopic procedures which have been in use for many years[20–22]. If bile duct injuries are more common in laparoscopic cholecystectomy, then the justification for its introduction will be seriously compromised. This study confirms that biliary tract surgery for calculous disease can be performed safely with low, acceptable, morbidity rates. Factors that may have contributed to the results include the large number of operations performed by consultants and the high and regular throughput during the study period.

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Laparoscopy in the management of pancreatic cancer: endoscopic cholecystojejunostomy for advanced disease

Following a period of animal experimentation in pigs, a laparoscopic technique for sutured gastrointestinal and bilioenteric anastomoses was developed and its safety and efficacy tested in chronic experiments. The method involves the construction of a preformed external jamming loop knot and continuous suturing using a specially developed Endoski needle. The technique was used to construct a cholecystojejunostomy in five patients with advanced cancer of the pancreas (four hand-sutured and one stapled/sutured). Four of the patients recovered from the procedure with no complications, minimal postoperative discomfort and complete relief of their jaundice. In one patient relief of jaundice was slow due to blockage of the anastomosis by debris and blood clot; this resolved following removal of the inspissated material. This minimally invasive procedure has the potential for complete palliation with short hospital stay and avoids the hazards of endoscopic stenting such as encrustation and cholangitis.

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During the past 2 years, an animal experimental programme has been in progress in this department designed to develop laparoscopic techniques of bilioenteric and gastrointestinal anastomosis. The results of these experiments have confirmed the safety and efficacy of these procedures. The technique used, and the outcome in the first five patients suffering from advanced cancer of the pancreas successfully treated by laparoscopic cholecystojejunostomy, are reported in this paper.

Patients and methods

All patients were women aged 71–84 (median 72) years with histologically proven cancer of the pancreas. Obstruction of the bile duct was complete, and bilirubin levels at presentation were within the range 160–460 μmol l^{-1}. Preoperative investigations included ultrasonographic examination of the liver and pancreas, computed tomography of the upper abdomen and endoscopic retrograde cholangiopancreatography (ERCP). In the first patient, a 9·0-cm, 7 Fr endoscopic stent was inserted through the tumour during the same ERCP session. This was followed by an initial rapid fall in the bilirubin level to 50 μmol l^{-1} within 5 days, but thereafter the patient experienced two episodes of cholangitis which resulted in marked deterioration in the results of liver function tests, with a rise in bilirubin to 280 μmol l^{-1}.

The findings at diagnostic laparoscopy confirmed the presence of inoperable disease: cancer of the head of the pancreas with hepatic deposits in four patients and a large carcinoma of the body of the pancreas in the fifth patient, who also had pulmonary deposits. All had large, tense, distended gallbladders. None had duodenal involvement by the disease or peritoneal deposits.

Technique of laparoscopic cholecystojejunostomy

Access. The telescope cannula (11·0 mm) is inserted in the immediate subumbilical region. The right suturing cannula (5·0 mm) is placed along the linea semilunaris well down almost at umbilical level, the left (5·0 mm) half way up the left paramedian plane. The fourth cannula (5·0 mm) is sited in the right hypochondrium close to the costal margin. This cannula is used by the assistant to hold the suture under tension while suturing is in progress.

Cholecystocholangiography and selection of jejunal loop. The patency of the cystic duct is initially confirmed by cholecystocholangiography performed using a Verres needle introduced through the fundus. After aspiration of the gallbladder bile, 50–70 ml 20 per cent sodium diatrizoate is injected to outline the biliary tract. This contrast examination is needed to confirm the patency of the cystic duct and the clearance of its insertion from the upper limit of the tumour by at least 2·0 cm (*Figure 1*). Thereafter, a loop of jejunum 60 cm from the ligament of Treitz is selected for anastomosis to the gallbladder after ensuring that it can be brought up antecolically to this organ without any tension.

Anastomosis. Hand suturing was performed in four patients and a combined stapling/suturing method in one patient. Suturing is performed with 3/0 coated polyglactin 910 (Vicryl; Ethicon, Edinburgh) mounted on an Endoski needle (Ethicon). A preformed jamming loop knot is fashioned externally on a 10·0-cm suture with the knot slipping from the tail. The suture is grasped by a 3·0-mm needle holder and loaded inside a suture applicator for introduction

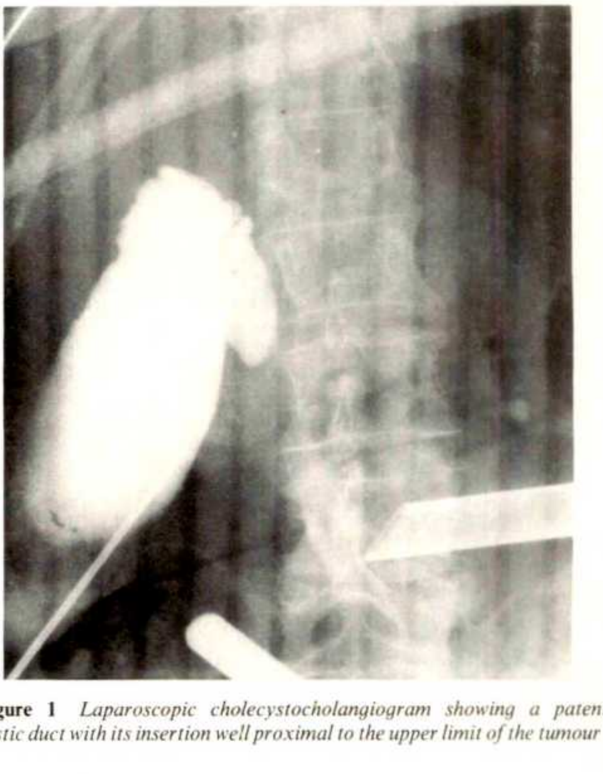

Figure 1 *Laparoscopic cholecystocholangiogram showing a patent cystic duct with its insertion well proximal to the upper limit of the tumour*

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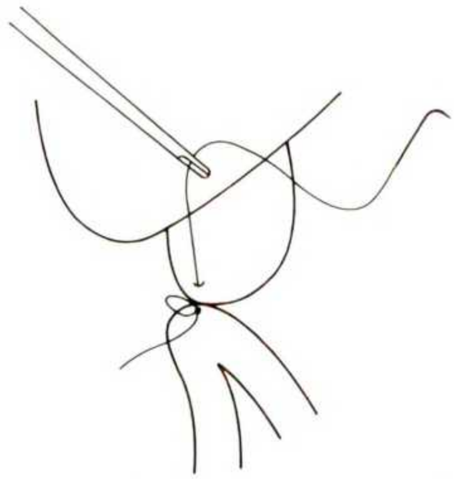

Figure 2 *After passage through the seromuscular layer of the jejunum and the gallbladder, the suture is pulled until the jamming loop knot impinges on the jejunum. The two organs are approximated with further traction on the suture*

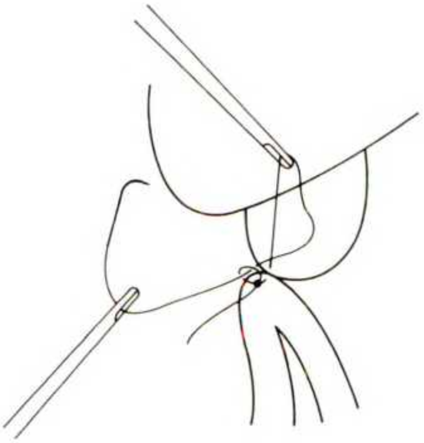

Figure 3 *While tension is maintained by the assistant, the suture is railroaded through the jamming loop*

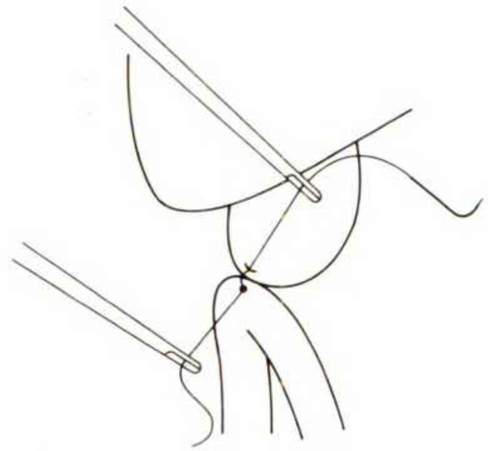

Figure 4 *The knot is then locked by slipping the tail against countertraction on the suture*

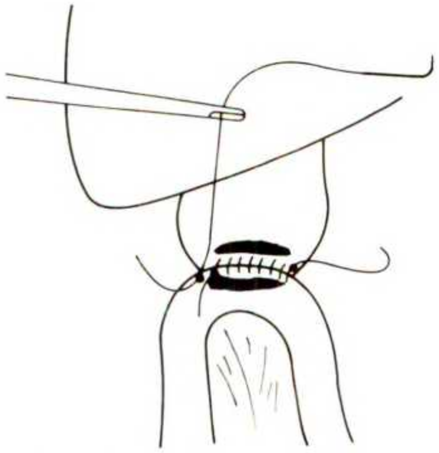

Figure 5 *After completion of the posterior suture line, the gallbladder and jejunum are opened. The first suture bite and jamming loop knot of the anterior layer are inserted lateral to the start of the posterior suture line*

into the peritoneal cavity. The needle is then grasped by the 5·0-mm needle holder and after passage through the seromuscular layer of the jejunum and the gallbladder, the suture is pulled until the jamming loop knot impinges on the jejunum. The two organs are approximated with further traction on the suture (*Figure 2*), and while tension on this is maintained by the assistant, the suture is railroaded through the jamming loop (*Figure 3*). The knot is locked by slipping the tail against countertraction on the suture (*Figure 4*).

A continuous posterior seromuscular approximation over a distance of 3·0 cm is next carried out with the assistant holding tension on the suture line. The suturing technique involves use of the 5·0-mm needle holder as the active driver with the 3·0-mm needle holder being used to apply contertraction on the tissue to facilitate needle passage and to pick up the needle after it emerges through the tissues before transfer to the active needle holder. The last but one suture bite is locked and, after a further passage of the needle through the two organs, the suture is tied using the Aberdeen knot, cut (leaving a long tail) and removed. The seromuscular layer of the gallbladder is then incised with the electrosurgical hook knife using a blender monopolar current (Erbe ACC-450, Tubingen, Germany) 0·5 cm anterior and parallel to the completed suture line. The mucosa is divided by twin-action scissors making a 2·0–3·0-cm opening. The gallbladder interior is aspirated and irrigated with Ringer's solution. The enterotomy is fashioned to an equivalent length and with the same technique. With the jejunum attached to the gallbladder, which keeps it tented high up, leakage from the enterotomy does not occur. The anterior wall of the anastomosis is constructed using a similar technique. The first suture and jamming loop knot are inserted lateral to the start of the posterior suture line (*Figure 5*). Once the end of the anterior approximation has been reached, the suture is tied to the tail of the Aberdeen knot using a standard microsurgical knot.

A different technique is used to perform a stapled/sutured anastomosis. Two stay sutures introduced through the anterior abdominal wall are inserted at the proposed limits of the anastomosis between the two organs. A small opening is then made on each organ. The EndoGIA (US Surgical, Norwalk, Connecticut, USA) is inserted, the stapler heads are approximated and the instrument is fired. After checking the stapled anastomotic line, the anterior defect is closed with a running suture as described above.

The mean time to carry out the anastomosis was 90 min.

Results

In line with our experimental observations, the postoperative period was uncomplicated in four patients. There was no abdominal distension and all patients passed flatus within 24 h. These four patients were discharged home by the tenth day. Postoperative analgesia requirements have been minimal, and the need for opiate medication was limited to the first 12 h after surgery.

In the patient undergoing stenting, the endoprosthesis was removed under antibiotic cover 3 days after surgery when the bilirubin had fallen to 50 μmol l^{-1}. This was immediately followed by an episode of cholangitis with a positive blood culture (*Escherichia coli*) and a rise in the bilirubin concentration to 200 μmol l^{-1}, but both settled quickly with treatment by systemic cefuroxime and metronidazole. The jaundice subsided completely thereafter.

Biliary scintigraphy has shown good function of the bilioenteric bypass. One patient subsequently received supervoltage radiotherapy, and two have required a percutaneous coeliac axis phenol nerve block for pain. The first patient has since died from disseminated disease. During the 3 months of survival, this patient did not require any hospital admissions and remained anicteric until the time of death.

In one patient the jaundice remained static after an initial fall. Percutaneous transhepatic cholangiography confirmed a blocked anastomosis. At reintervention, blockage by debris and blood clot of a 2·0-cm anastomosis was found and this was evacuated through a small cholecystotomy which was then sutured. The jaundice cleared rapidly after this procedure.

Discussion

The reported experience on diagnostic laparoscopy has shown the value of this technique in the diagnosis of hepatobiliary disease and obstructive jaundice[1-5] and in the staging of intra-abdominal malignancy, particularly pancreatic cancer[6-13]. The authors of most of these series have concluded that laparoscopy is superior to ultrasonography and computed tomography in the detection of small hepatic deposits and peritoneal involvement. This diagnostic modality, which has been in long usage in our institution, confers undoubted benefit to patients with pancreatic cancer since it avoids unnecessary laparotomy in patients with advanced disease while permitting visualization of the tumour by either the supragastric or infragastric approach[9,14,15], with procurement of biopsy material for histological confirmation of the diagnosis.

The new development of laparoscopic cholecystojejunostomy is a logical extension of the use of diagnostic laparoscopy in this condition and provides good and efficient palliation of biliary obstruction in patients with advanced pancreatic malignancy, avoiding the need for readmissions necessitated by endoprosthesis-related complications. A double bypass consisting of an antecolic gastroenterostomy in addition to the bilioenteric anastomosis is technically possible and has been evaluated experimentally in this institution. Gastroenterostomy was not performed in these patients because they had no evidence or symptoms of duodenal obstruction. As in open surgery, laparoscopic cholecystojejunostomy is indicated when the junction of the cystic and common hepatic ducts is well clear of the tumour. Otherwise a hepaticojejunostomy is performed. It is not possible at this stage to make any valid comparisons between the sutured and stapled techniques. The time taken is the same, and the stapling method still requires that the surgeon is proficient in laparoscopic suturing techniques.

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Case report

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Gastric emphysema following drug-induced gastritis

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A case of intramural air in the stomach with pneumoperitoneum due to gastric emphysema which was managed conservatively is presented.

Case report

A 55-year-old man presented as an emergency with a 10-day history of pain in the upper abdomen with distension, vomiting and hiccoughs. He had suffered from gouty arthritis for 25 years and from mild diet-controlled diabetes mellitus. The patient was taking non-steroidal anti-inflammatory drugs for a recent exacerbation of arthritis.

On examination there was tachycardia, fullness in the epigastrium and tenderness in the upper abdomen. Laboratory investigation showed leucocytosis (white cell count 12×10^9/litre) and a blood glucose level of 13·75 mmol/l. A nasogastric tube was passed and approximately 2 litres of haemorrhagic aspirate was obtained, which completely relieved the distension and pain. The abdomen became soft and non-tender.

A diagnosis was made of acute gastric dilatation following drug-induced gastritis and continuous Ryle's tube suction was maintained.

Erect abdominal radiography showed a dilated stomach with a characteristic linear pattern of gas in the stomach wall (*Figure 1a*). There was also a small amount of air under the right hemidiaphragm (*Figure 1b*). Conservative management was continued with nasogastric aspiration and antibiotics, as the patient's clinical condition had improved and there was no sign of peritonitis.

Recovery was uneventful. Repeat abdominal radiography on the 13th day showed complete resolution of intramural and subphrenic air. Gastroscopy 3 weeks later showed gastritis with a few antral erosions. H_2-receptor antagonists were prescribed.

Discussion

Lee and Rutledge[1] reviewed 41 cases of intramural air in the stomach with regard to the mechanism of the lesion and its clinical course. Gastric emphysema presents with a linear pattern of gas shown by radiography and follows a benign clinical course, in contrast to emphysematous gastritis which is due to gas-forming infection of the stomach wall. This condition presents with bubbles, or streaks or mottled radiolucencies, has a difficult clinical course and frequently results in death[1]. Emphysematous gastritis may also present with linear gas shadows[2], and cystic radiolucencies have occasionally been found in the stomach due to non-bacterial causes[3,4].

In general, it is accepted that gastric emphysema is due to air being forced into the wall of the stomach through a break in the mucosa, into the submucosa or subserosa. Vomiting and endoscopic insufflation can force air into the stomach wall, especially if there is a mucosal defect due to ulcer, carcinoma or other causes[1].

In this patient, the mucosal defect was produced by drug-induced gastritis with erosions; gastric dilatation and vomiting could have forced air into the stomach wall. The gas under the diaphragm is due either to subserosal seepage of air under the diaphragmatic peritoneum or to rupture of a subserosal bleb. In this patient, the linear gas pattern on radiography suggested the diagnosis of benign gastric emphysema. The prompt relief obtained by conservative measures, the lack of abdominal signs and rapid clinical recovery confirmed this diagnosis. Pneumoperitoneum in such patients should be interpreted in the light of the clinical condition and response. Gastric emphysema can be expected to resolve rapidly with conservative management.

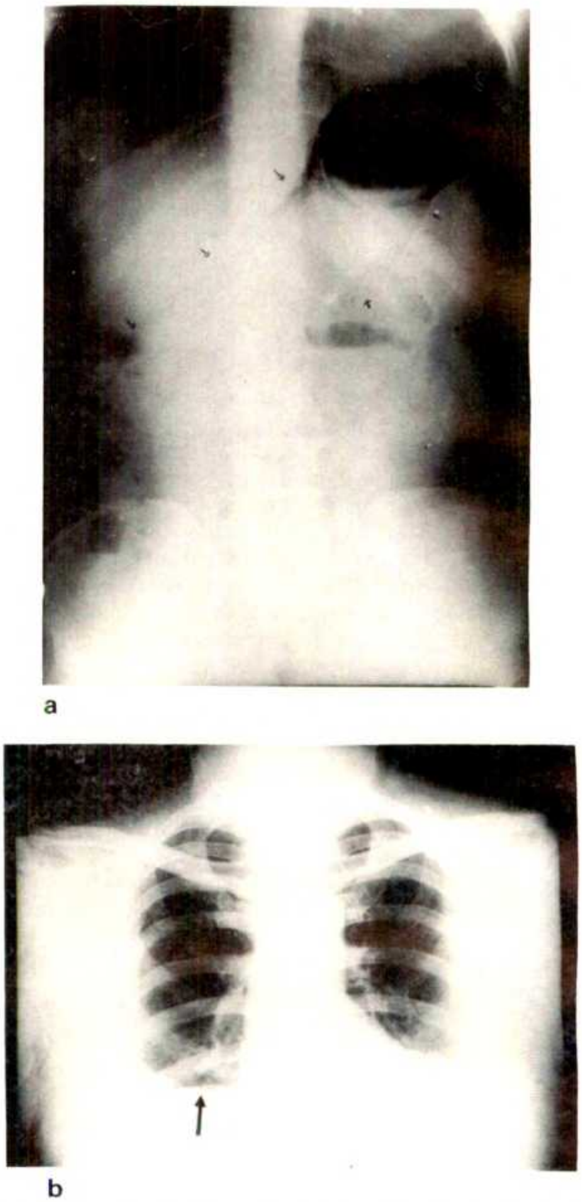

Figure 1 *Abdominal radiographs showing* **a** *dilated stomach outlined by linear intramural gas shadow (arrows);* **b** *air under the right hemidiaphragm (arrow)*

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Metabolic bone disease following gastrectomy: assessment by dual energy X-ray absorptiometry

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Although disorders in bone metabolism have long been recognized as typical sequelae of gastrectomy, there has until now been no reliable method of providing precise assessment of bone mass, resulting in a variation of reported incidence. In this study, metabolic bone disease was evaluated in a well characterized population: 34 men 2–5 years after gastrectomy; 11 men 6–10 years after gastrectomy; eight men 2–5 years after colonic resection; and 115 healthy men. The age range was 50–69 years. An innovative reliable method of dual energy X-ray absorptiometry was used which allows quantitative assessment of bone mineral content. Measurement of lumbar spine bone mineral density revealed that the mean(s.e.m.) bone mineral density in patients who had had a gastrectomy (2–5 years 0·84(0·03) g/cm^2, 6–10 years 0·85(0·05) g/cm^2) was significantly lower than that of patients who had undergone colonic resection (0·96(0·04) g/cm^2) or healthy men (0·96(0·03) g/cm^2). This study demonstrates that a high incidence of bone atrophy is induced at the relatively early period of 2–5 years after gastrectomy.

Although metabolic bone disease has long been recognized as a common sequel of gastrectomy[1–14], most investigations of postgastrectomy bone disease have dealt with heterogeneous populations, sometimes including both sexes, widely disparate ages, and varying periods of follow-up. Age- and sex-matched controls must be taken into consideration when evaluating bone atrophy subsequent to gastrectomy, since it is universally recognized that metabolic bone atrophy is observed physiologically with increasing age in both men and women[15,16], and could especially be affected by changes in hormone levels in women[16]. Furthermore, techniques for characterizing bone atrophy have often been inadequate, resulting in variation in the reported incidence of postgastrectomy metabolic bone disease, ranging from 1 to 50 per cent[2,4,6,8,10,14]. Dual photon absorptiometry[17–19] is a widely used technique for measuring bone mineral mass. It has, however, been recently demonstrated that dual energy X-ray absorptiometry[20–22], a new dual energy non-invasive radiological technique, is a superior method of quantifying bone mineral content compared with dual photon absorptiometry. The current study was performed to determine whether gastrectomy is significantly associated with metabolic bone disease in a well characterized population using this new method.

Patients and methods

Eligible subjects were men with gastric cancer who had undergone curative gastrectomy 2–5 years previously and who at the time of the study were between 50 and 69 years old. Patients were excluded if they had any other potential cause of altered bone and mineral metabolism, such as chronic alcoholism, renal failure, small bowel or pancreatic or liver disease, small bowel resection, endocrinopathy, or steroid or vitamin D therapy. Thirty-four patients with gastrectomy were selected for study. Operative procedures were as follows: subtotal gastrectomy with Billroth I reconstruction (24 patients), with Billroth II reconstruction (two patients), total gastrectomy with Roux-en-Y reconstruction (eight patients). A total of 115 healthy men between the ages of 50 and 69 years (69 between 50 and 59 years, 46 between 60 and 69 years) who were participating in a concurrent normative study of bone mineral content served as controls. Eight men with cancer of the colon who had undergone curative colonic resection 2–5 years previously, and who at the time of the study were aged between 50 and 69 years, were examined for comparison. Operative procedures for these were as follows: partial colonic resection (six patients), right hemicolectomy (two patients). Eleven men with gastric cancer between the ages of 50 and 69 years who had undergone curative gastrectomy 6–10 years previously were also examined to investigate the relationship between bone atrophy and time after gastrectomy. Operative procedures here were subtotal gastrectomy with Billroth I reconstruction (eight patients) and total gastrectomy with Roux-en-Y reconstruction (three patients).

In addition, 196 healthy men whose ages were outwith the sixth and seventh decades (20–29 years, 32 men; 30–39 years, 56 men; 40–49 years, 72 men; 70–79 years, 22 men; 80–89 years, 14 men) were examined to investigate the relationship between bone atrophy and age. Care was taken to ensure that none of the patients who participated in this study had any of the above exclusion criteria. None of the healthy men who served as controls had undergone laparotomy. It was confirmed during the investigation that no recurrence of disease was apparent clinically in the patients who had undergone gastrectomy or colonic resection. Informed consent was obtained from all participants and investigations were carried out in accordance with the World Medical Association Declaration of Helsinki, adopted in 1964 and amended in 1975, 1983 and 1989.

Assessment of bone mineral content

Bone mineral content was assessed by determination of L2–L4 lumbar spine bone mineral density (BMD) in grams per square centimetre. Dual energy X-ray absorptiometry was performed with a Hologic (Waltham, Maryland, USA) model QDR-1000 bone densitometer. The dual energy bone densitometer utilizes an X-ray tube, driven by a dual voltage pulsed power supply, as the photon source. This source provides approximately 500 times more photon flux than the $3{\cdot}7 \times 10^{10}$ Bq (1 Ci) gadolinium-153 sources typically used in bone mineral analysers. The flux increase was exploited to improve scan resolution, reduce imaging time, and improve precision. The system alternates between low and high energy, and between patient and reference measurements, on a pixel-by-pixel basis. This device compensates for power supply and detector variations, adjusts for spectral effects such as hardening of the X-ray beam by soft tissues, and obviates the need for periodic external calibration. The photon source is a tungsten stationary-anode X-ray tube, pulsed alternately to a peak kilovoltage (kV$_p$) of 70 and 149, and operated at a peak tube current of about 3 mA. Aluminium half-value-layer measurements were used to determine effective beam energies of 43 keV and 110 keV. The 70 kV$_p$ filtration is 2 mm aluminium, and the 140 kV$_p$ filtration employs an additional 1·6 mm

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brass. This model has a 2·3-mm source collimator, a single detector located 45 cm above the scanning table, and a transverse scanning of 60 mm/s. Contiguous transverse scans were separated by 1-mm increments in the longitudinal direction. This system is capable of determining the BMD of the lumbar spine with a 5-min scan time, an entrance exposure of under 3 mR, and a precision of better than 0·01 g/cm^2 (coefficient of variation 1 per cent at a density of 1·00 g/cm^2).

Radiographic diagnosis of bone atrophy

The grade of bone atrophy was diagnosed by radiography in 28 patients with gastric cancer aged from 50 to 69 years who had undergone gastrectomy 2–5 years previously. The grade of bone disease was based on the classification of radiological atrophy of the third lumbar vertebra by Itami and Ohatake[23]. This classification is as follows: early stage, general reduction of bone density; grade 1, reduction of horizontal trabeculae with conspicuous longitudinal trabeculae; grade 2, more reduction of horizontal trabeculae and rough longitudinal trabeculae.

Microdensitometric evaluation of bone atrophy

Radiological studies on both hands were performed in 23 patients with gastric cancer aged from 50 to 69 years who had undergone gastrectomy 2–5 years previously, using an aluminium step wedge (Gray scale). Measurements were made at the mid-portion of the second metacarpal bone by the microdensitometric method of Inoue *et al.*[24]. The density of the bone was expressed qualitatively as the metacarpal index, the ratio of cortex width to bone width.

Laboratory examination

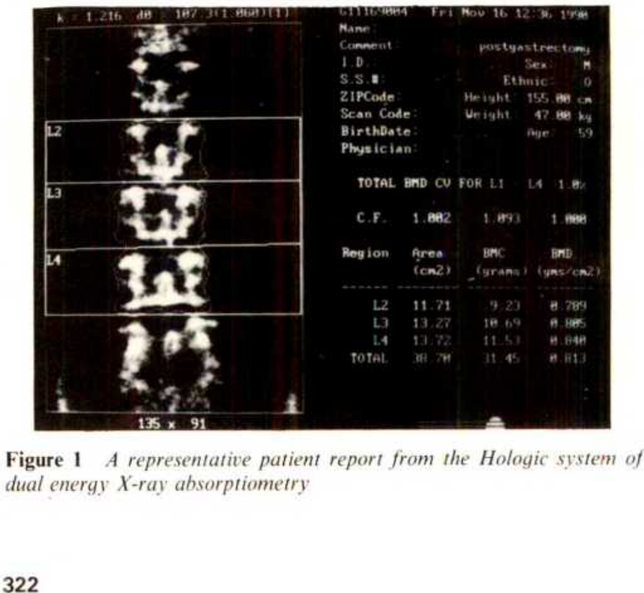
In 34 patients aged from 50 to 69 years who had had gastric cancer and who had undergone gastrectomy 2–5 years previously, peripheral blood was taken to measure serum levels of substances related to bone metabolism, including calcium, phosphorus and alkaline phosphatase.

Analysis of data

Results are expressed as mean(s.e.m.). For statistical analysis, Student's *t* test or analysis of variance was used, and a *P* value $<0·05$ was considered significant.

Results

Figure 1 shows a representative result from the Hologic system of dual energy X-ray absorptiometry, illustrating calculation of BMD for L2, L3 and L4 and for the three levels combined. Assessment of metabolic bone atrophy by dual energy X-ray absorptiometry revealed that BMD decreased with increasing age (*Figure 2*). Although no significant difference was found between mean(s.e.m.) BMD in the sixth decade, 0·95(0·02) g/cm^2, and in the seventh decade, 0·97(0·03) g/cm^2, BMD showed a significant and sharp decrease to 0·87(0·04) g/cm^2 between 70 and 79 years (*Figure 2*). Comparative study of BMD in 34 patients who had had gastric cancer and eight who had had cancer of the colon, all of whom were aged between 50 and 69 years and who had undergone gastrectomy or colonic resection 2–5 years previously, indicated that BMD in patients who had undergone gastrectomy was significantly lower than that in those who had had colonic resection (*Figure 3*). BMD in patients with colonic resection showed a similar distribution to that observed in healthy men. On the other hand, of the 34 patients who had had a gastrectomy, 15 (44 per cent) had very low values of $<0·8$ g/cm^2 (*Figure 3*).



```
                     Fri Nov 16 12:36 1990
Name:
Comment:             postgastrectomy
I.D.:                         Sex:   M
S.S.#:                     Ethnic:   0
ZIPCode:           Height  155.00 cm
Scan Code:         Weight   47.00 kg
BirthDate:                   Age:   59
Physician:

   TOTAL BMD CV FOR L1 - L4  1.0%

   C.F.    1.002     1.093     1.000

Region    Area       BMC        BMD
          (cm2)    (grams)  (gms/cm2)
------  -------   -------   --------
    L2    11.71      9.23      0.789
    L3    13.27     10.69      0.805
    L4    13.72     11.53      0.840
 TOTAL    38.70     31.45      0.813
```

Figure 1 *A representative patient report from the Hologic system of dual energy X-ray absorptiometry*

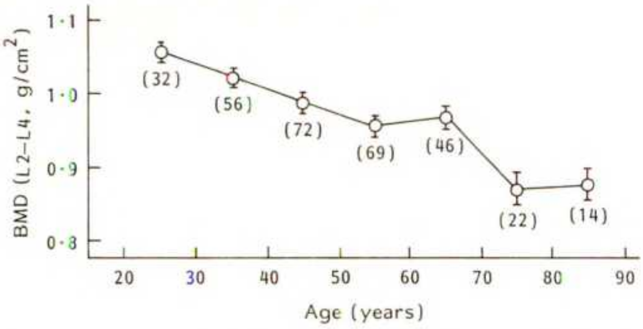


Figure 2 *Bone mineral density (BMD) in 311 healthy men in relation to age. Values are mean(s.e.m.); values in parentheses are numbers in each decade*

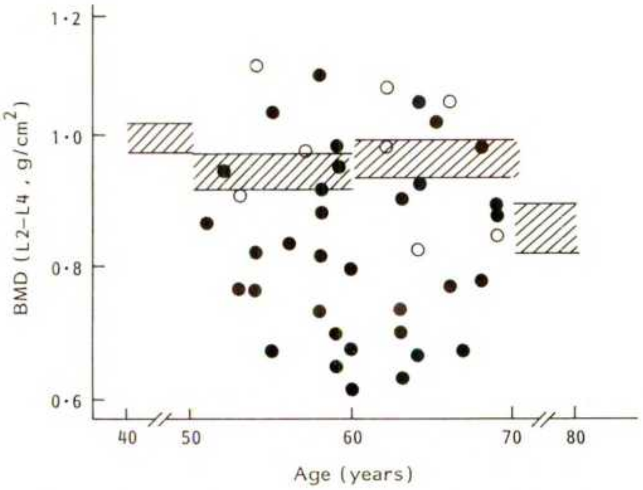


Figure 3 *Bone mineral density (BMD) in 34 patients who had had gastric cancer and eight who had had cancer of the colon. Both groups were of age 50–59 years and had undergone gastrectomy (●) or colonic resection (○) 2–5 years previously. The shaded line indicates mean(s.e.m.) BMD values in healthy men in each decade (sixth decade,* n = *69; seventh decade,* n = *46)*

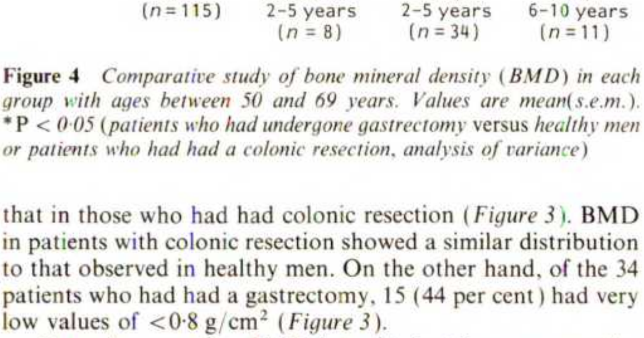


Figure 4 *Comparative study of bone mineral density (BMD) in each group with ages between 50 and 69 years. Values are mean(s.e.m.).* *$P < 0·05$ *(patients who had undergone gastrectomy* versus *healthy men or patients who had had a colonic resection, analysis of variance)*

Figure 4 summarizes BMD data obtained from comparative study of each group with ages between 50 and 69 years. No significant difference was noted between BMD in healthy men, 0·96(0·03) g/cm^2, and BMD in patients with colonic resection, 0·96(0·04) g/cm^2. BMD in 34 patients 2–5 years after gastrectomy, 0·84(0·03) g/cm^2, and in 11 patients 6–10 years after gastrectomy, 0·85(0·05) g/cm^2, was significantly lower than that measured in healthy men or in patients who had had colonic resection. There was, however, no significant difference between BMD in patients 2–5 years after gastrectomy and in those 6–10 years after gastrectomy. Comparative data on BMD with special reference to the reconstruction procedure are as follows: subtotal gastrectomy with Billroth I reconstruction 0·86(0·04) g/cm^2 $(n = 24)$; with Billroth II reconstruction 0·86(0·01) g/cm^2 $(n = 2)$; total gastrectomy with Roux-en-Y reconstruction 0·81(0·06) g/cm^2 $(n = 8)$ in patients 2–5 years after gastrectomy; and subtotal gastrectomy with Billroth I reconstruction 0·86(0·05) g/cm^2 $(n = 8)$, total gastrectomy with Roux-en-Y reconstruction 0·83(0·20) g/cm^2 $(n = 3)$ in patients 6–10 years after gastrectomy. No significant difference was found in BMD with respect to the operations. Results from the diagnostic radiological study on bone atrophy in 28 patients who had had a gastrectomy were as follows: early stage $(n = 6)$, grade 1 $(n = 8)$ and grade 2 $(n = 1)$. Microdensitometric study of bone atrophy revealed that the mean(s.e.m.) value of metacarpal index in 23 gastrectomized patients was relatively low at 0·40(0·014), normal range 0·40–0·55. Eight patients (35 per cent) had values of $<0{\cdot}37$, ranging from 0·28 to 0·37. The laboratory data for mean(s.e.m.) serum levels of calcium, 8·74(0·08) mg/dl, phosphorus, 3·65(0·16) mg/dl, and alkaline phosphatase, 48·8(3·0) units/l, were all within the normal ranges in the 34 patients who had had a gastrectomy 2–5 years ago.

Discussion

Among the complications of gastrectomy, metabolic bone disease involving a decrease in bone mass, expressed as bone atrophy or osteopenia, is universally recognized. Nevertheless, the reported incidence of postgastrectomy metabolic bone disease has varied widely, chiefly because of the difficulty in the quantitative evaluation of bone atrophy. At present, the most widely used techniques of measuring BMD include single photon absorptiometry[18,25], dual photon absorptiometry[17–19], and quantitative computed tomography[26,27]. Single photon absorptiometry is currently used to measure bone mineral content of the distal radius and os calcis. However, one of the problems is that measurements made at these anatomical sites do not correlate well with measurements made in the spine and hip, which are much more important sites of fracture in osteopenic states[25]. Quantitative computed tomography can measure only the spine without sophisticated data processing, involves high radiation doses, and is subject to measurement errors due to varying fat content of the marrow[27]. Dual photon absorptiometry, which is capable of measuring an integral of cortical and trabecular bone in the spine or hip, has less than ideal precision, problems with image spatial resolution, periodic expensive source replacement, and a long examination time (20–30 min per site)[19]. The newly developed non-invasive method of dual energy radiographic absorptiometry[20–22] has been introduced recently in response to these difficulties in measurement. This new technique uses an X-ray rather than radioisotope source and consequently has higher resolution and greater speed than dual photon absorptiometry. One of the major advantages associated with the use of an X-ray over a radioisotope source is its intensity. An X-ray source with an average tube current of 1 mA produces 500–1000 times more photon flux than does the $3{\cdot}7 \times 10^{10}$ Bq (1 Ci) gadolinium-153 source used in the conventional dual photon absorptiometry system. Dual photon absorptiometry gives an inaccurate identification of intervertebral spaces on low resolution images[21], whereas dual energy radiographic absorptiometry exhibits an approximately threefold greater precision in phantom, specimen and patient studies[22], a feature that is expected to enhance significantly the clinical usefulness of projectional densitometric procedures.

The present study has demonstrated that BMD in men after gastrectomy is significantly lower than that in age-matched healthy male controls, or in age-matched men after colonic resection. Furthermore, this is the first study to demonstrate an unexpectedly high incidence of bone atrophy, with considerably low BMD, at a relatively early time after gastrectomy. Both radiographic examination and microdensitometric evaluation also showed a high incidence of bone atrophy 2–5 years after gastrectomy in the same men. In addition, the study revealed that there is no significant difference in BMD between those patients 2–5 years after gastrectomy and those 6–10 years after gastrectomy, suggesting that an increased incidence of bone atrophy is induced within 5 years of operation. This, in turn, may imply the desirability of periodic examination of changes in BMD from a relatively early stage after gastrectomy. Although most of the gastrectomized patients with bone atrophy in the present study were asymptomatic and the clinical significance of the data presented remains to be elucidated, the possibility remains that this latent bone disease will become manifest with time.

Both osteomalacia and osteoporosis have been suggested as components of postgastrectomy bone disease[7,8]. The pathogenesis of osteoporosis, however, has not been explained as satisfactorily as that of osteomalacia, which has been regarded as the major component of bone disease in patients after gastrectomy[6,8,10,28]. The most widely used and the simplest screening test for the detection of postgastrectomy osteomalacia is the estimation of serum alkaline phosphatase. The normal serum alkaline phosphatase level in the present patients 2–5 years after gastrectomy may suggest that reduction in BMD is due not to osteomalacia, but to osteoporosis. The radiological grading results in the present study might also support the notion of osteoporosis[23]. However, the possibility cannot be denied that the changes of osteomalacia might be found in patients 6–10 years after gastrectomy, since no determination of serum alkaline phosphatase levels was performed in these patients.

Persuasive explanations for the aetiology of postgastrectomy metabolic bone disease have yet to be given. Among many causal factors, malabsorption of vitamin D and/or calcium has been suggested as the main cause[2,5–7,9,28]. The pathophysiology of metabolic bone disease after gastric surgery involves alterations in vitamin D metabolism[13,29–31]. Concerning the comparative study on changes in bone mineral content after different operative procedures, there is no general agreement that bone disorders are more common after Billroth II gastrectomy than after Billroth I gastrectomy. No differences have been shown in osteomalacia occurring after Billroth I and II gastrectomy[6], no differences in radiological spinal rarefaction between Billroth I and II gastrectomy[7], and no differences in bone density between Billroth I and II gastrectomy[10], except one report that observed greater bone atrophy after Billroth II than after Billroth I gastrectomy[14]. Nilas *et al.*[29] demonstrated that gastrectomized patients with Billroth I reconstruction had hypocalcaemia, raised serum alkaline phosphatase levels, and reduced bone mineral content, whereas bone mineral content was normal in patients who had undergone Billroth II gastrectomy in spite of the presence of the same biochemical disturbances. It is noteworthy that there is more evidence that bone disorders are commoner after total gastrectomy[14,31,32]. In the present study, although BMD in eight patients 2–5 years after total gastrectomy was less than that in 24 patients 2–5 years after Billroth I gastrectomy, this difference was not statistically significant, probably because of the small number of patients with total gastrectomy. Studies on calcium balance and enterohepatic circulation of vitamin D metabolites following gastrectomy[29–31,33] would be helpful in elucidating the mechanism for any such differences between operative procedures.

Acknowledgements

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Splenic salvage using an absorbable mesh: feasibility, reliability and safety

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Forty-nine adults underwent surgery for splenic injury: 17 (group 1) had salvage with a splenic mesh, seven (group 2) underwent other preservation techniques, and 25 (group 3) underwent splenectomy. There were six, zero and 11 hilar lesions in groups 1, 2 and 3, respectively. Seven of 15 associated lesions involved the digestive tract. There was no significant difference in transfusion requirements, length of operation or postoperative complications. One patient died in each of groups 1 and 2, and eight in group 3. Secondary splenectomy was performed once in groups 1 and 2. The duration of hospital stay was shorter in the preservation groups (1 and 2) than in group 3. Splenic preservation was feasible in 24 of 49 adults with splenic injury requiring surgery. The splenic mesh wrap is safe and reliable, and allows splenic salvage even with hilar injury.

The spleen should not be sacrificed frivolously after trauma[1,2]. The rationale for splenic preservation[3] and the success of salvage in children has prompted surgeons to adopt the same policy in adults[2–4]. The capsule of the adult spleen is reputed to be less elastic and robust than that in the child[5] and surgeons have been hesitant to apply splenorrhaphy techniques[6]. Other methods have included reinforcement of sutures by the ladder technique[7], pledgets[7], falciform ligament[8] and omentum[7,9]. More recently, an absorbable mesh, derived from one designed for kidney injury, has become available and early experience with splenic salvage has been described[10–17]. This study describes the use of absorbable mesh in one institution in the preservation of the injured adult spleen.

Patients and methods

Patients

Records of patients with an injured spleen seen between October 1985 and September 1990 were reviewed. Patients were excluded if: (1) they were under 15 years old; (2) bleeding was arrested by simple intraoperative compression; (3) they had iatrogenic intraoperative injury; (4) they had underlying pathology; (5) the main splenic artery was ligated or embolized; or (6) they were managed non-operatively.

Information included the type of splenic injury, the time elapsed between accident and operation, the results of preoperative investigations, patient haemodynamics and the amount of fluid replacement, associated lesions, time to obtain complete haemostasis, operative times, postoperative course, duration of hospital stay and outcome.

Operative management

A midline incision was used in all cases except one (stab wound extended to a subcostal approach). Splenic and associated intra-abdominal lesions were identified and treated according to priorities. The spleen was freed from its gastric, phrenic and mesocolic attachments. If the technique of mesh salvage was to be used, subcapsular haematoma was evacuated and all devascularized segments were removed. The synthetic mesh was placed around the convexity of the mobilized spleen. Polyglactin mesh with purse-string (Ethicon, Paris, France)[11] or a polyglycolic acid mesh, threaded during operation with purse-string sutures (Davis and Geck, Rungis, France), was tightened from edge to centre. If bleeding did not stop, the surgeon made supplementary sutures and added topical haemostatic agents or a second mesh.

The left subphrenic space was not drained. Calcium heparinate was initiated in the immediate postoperative period and discontinued once the patient was fully ambulant or postsplenectomy thrombocytosis had subsided. Perioperative antibiotic prophylaxis involved the use of cephalosporins for 24 h.

Results

Forty-nine patients were seen during the 60-month period (36 men and 13 women) with a mean age of 30·2 (range 15–80) years. All but one injury was due to blunt trauma. The sex and age distribution of patients and the type of accident are shown in *Table 1*. Splenic salvage was attempted in 24 patients; 17 of these had a splenic wrap (two after partial splenectomy) and form group 1. During the same period, seven patients had a splenic preservation by splenorrhaphy or coagulation (group 2) and 25 patients underwent splenectomy (group 3).

The time from injury to operation did not vary significantly between the three groups. Preoperative ultrasonography was performed in 41 of the 49 patients and identified splenic injury in 37. Peritoneal lavage and computed tomography were employed in only four and three cases, respectively. Eight patients (three in group 1, one in group 2 and four in group 3) were operated on without preoperative investigations other than peritoneal lavage because of obvious intra-abdominal bleeding or precarious haemodynamic status. The distribution

Table 1 *Patient details*

	Group 1	Group 2	Group 3	Total
No. of patients	17	7	25	49
Type of accident				
Traffic	13	6	15	34
Work	2	0	4	6
Domestic	1	0	3	4
Fall	0	0	2	2
Aggression	1	1*	1	3
Mean (range) age (years)	26·4 (15–52)	29·1 (21–67)	32·0 (15–80)	30·2 (15–80)
Sex ratio (M:F)	13:4	6:1	17:8	36:13

*Stab wound

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Table 2 *Organ injury scaling: the Splenic Injury Scale (American Association for the Surgery of Trauma)*[18]

Grade*		Injury description†	Group 1 ($n = 17$)	Group 2 ($n = 7$)	Group 3 ($n = 25$)
I.	Haematoma	Subcapsular, non-expanding, < 10 per cent of surface area		2	
	Laceration	Capsular tear, non-bleeding, < 1 cm parenchymal depth			
II.	Haematoma	Subcapsular, non-expanding, 10–50 per cent of surface area Intraparenchymal, non-expanding, < 2 cm in diameter	5	5	6
	Laceration	Capsular tear, active bleeding, 1–3 cm parenchymal depth which does not involve a trabecular vessel			
III.	Haematoma	Subcapsular, > 50 per cent of surface area or expanding Ruptured subcapsular haematoma with active bleeding Intraparenchymal haematoma > 2 cm or expanding	6		5
	Laceration	> 3 cm parenchymal depth or involving trabecular vessels			
IV.	Haematoma	Ruptured intraparenchymal haematoma with active bleeding	6		6
	Laceration	Laceration involving segmental or hilar vessels producing major devascularization (> 25 per cent of spleen)			
V.	Laceration	Completely shattered spleen			8
	Vascular	Hilar vascular injury which devascularizes spleen			

*Advance one grade for multiple injuries to the same organ; †based on most accurate assessment at autopsy, laparotomy or radiological study

Table 3 *Presence of other intra-abdominal and/or extra-abdominal lesions*

	Intra-abdominal	Extra-abdominal	Isolated (spleen only)	Total no. of lesions*
Group 1 ($n = 17$)	4 (2)	11	8	32
Group 2 ($n = 7$)	1 (0)	3	4	11
Group 3 ($n = 25$)	10 (5)†	17	3	52

Values in parentheses are numbers of enteric injuries. *Number of cases of splenic injury plus total number of other (intra- or extra-abdominal) injuries; †without contamination in two cases

of lesions according to their type[18] is shown in *Table 2*. Other intraperitoneal and extraperitoneal associated lesions are listed in *Table 3*. As can be seen in *Table 4*, the mean time to obtain complete haemostasis did not differ significantly between groups. Total fluids infused did not differ significantly between the three groups (mean(s.d.) 4953(3186), 5342(3961) and 6892(4539) ml, respectively).

There were ten deaths. Two intraoperative deaths occurred in group 3. Two patients with splenic salvage and six undergoing splenectomy died within 30 days or during the same period of hospitalization from multiple organ failure (one exception). One patient in group 2 died from septic complications after surgical treatment of type I splenic lacerations, hepatic and intestinal trauma. There were no deaths related directly to splenic salvage.

Secondary splenectomy was required in two patients undergoing initial preservation. There were two cases of serous, non-infected perisplenic effusions in group 1, one of which was drained percutaneously; the other regressed spontaneously. There were no overt septic complications following splenic salvage with the mesh whereas subphrenic abscess occurred in three patients undergoing splenectomy. Postoperative pulmonary complications occurred in one, zero and five patients in groups 1, 2 and 3, respectively. There were three wound abscesses, one in group 2, and two in group 3. Of 49 patients operated on, 22 spleens were salvaged.

Hospital stay was shorter in those patients undergoing preservation. One patient in each of groups 1 and 3 developed an incisional hernia.

Discussion

The injured spleen is capable of healing, and can be repaired and partially resected safely[1,4,7]. The techniques currently available for preservation and/or haemostasis have been reviewed by Shackford and Molin[1], Perry[4], Butain and Gould[7], and Feliciano *et al.*[19].

Absorbable mesh wrapped around the spleen ensures haemostasis by tamponade and provides a safe, easy and reliable method of preserving the normal architecture and vascular supply[19–22] of the spleen within the portal circulation[10], conditions that affect adequate splenic function[22–24]. The method of Lange *et al.*[12] and others[14,15] described the mobilized spleen passing through a hole in the centre of the mesh which was then tightened. In this study the mesh was applied as a hair-net placed circumferentially around the convexity of the organ[10,11,25]. This method was first described in the dog by Delany *et al.*[10], and by 12 weeks the mesh, no longer visible, was replaced by a new capsule. Lange *et al.*[12] reported the use of a splenic wrap in nine of 22 salvage

Table 4 *Duration of operation, time spent on spleen, hospital stay and total infusion requirement*

	Mean(s.d.) duration of operation (min)	Mean(s.d.) time spent on spleen (min)	Median (range) length of hospital stay (days)	Mean (range) total infusion requirement (ml)
Group 1 ($n = 17$)	226·2(159·1)*	95·7(82·7)*	10 (3–20)	4953 (250–7000)
Group 2 ($n = 7$)	217·4(143·7)	125·4(116·4)	9 (3–19)	5342 (250–8500)
Group 3 ($n = 25$)	238·0(151·4)	81·7(37·6)	16 (4–78)	6892 (500–19 500)

*A second splenic wrap was added in two patients procedures and recommended this technique for extensive or deep parenchymal injuries involving the hilum. The present salvage rate for this injury is very low[3,12,26,27]. Some have limited the indications for splenic wrap to capsular avulsions and bleeding subcapsular haematoma[14,16]. We and others[11,12,25] believe that the spleen with certain hilum injuries (*Table 2*) can be salvaged with this technique.

Another contraindication to salvage has been continued bleeding[3,27]. Adding sutures or a second mesh (*Table 4*) have always been adequate measures to maintain preservation[11]. In accordance with others[11,15,25,28,29], these data (*Table 4*) do not suggest that extra time is needed to achieve haemostasis or that the procedure increases blood transfusion requirements. Splenic salvage should be attempted only once the spleen has been fully mobilized and the pedicle clamped to minimize intraoperative blood loss.

The advantages of splenic salvage in the multiple injury setting were addressed by Giuliano and Lim in 1981[29]. Thirty-three patients were managed with splenic salvage, 18 of whom had associated lesions and were treated without increased postoperative morbidity. The procedure has been used successfully in this setting by others[11,25,30] without increased morbidity or mortality rates or operative time. In this series, splenic salvage was successful in 12 patients with a total of 43 injuries (*Table 3*). No complications were directly linked to the procedure. Splenic preservation should be attempted with caution in patients with poor prognosis, especially when there is head or spinal injury[1,2,31]. A relative contraindication to splenic salvage has been concomitant bowel injury[31]. In several retrospective studies[7,31,32], post-traumatic sepsis was more frequent after splenectomy associated with other intra-abdominal (colonic) injuries. As in other reports[1,17,25], the use of a splenic wrap was not associated with increased infection. Splenic salvage with the mesh can be safe, with little evidence of rebleeding despite anticoagulant therapy (results from this series and References 11, 22 and 33). Splenic repair is feasible as a standard procedure in a district general hospital[11,17,34,35].

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Gastric involvement of oesophageal squamous cell carcinoma

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Among 402 patients with squamous cell carcinoma of the oesophagus, gastric wall involvement was evident in 32 (8·0 per cent). These could be grouped into four types according to the pattern of involvement: group 1 included six patients with gastric involvement via metastases in perigastric lymph nodes; group 2 consisted of 11 patients with gastric intramural metastasis; group 3 contained 12 with direct invasion of the gastric wall by the oesophageal squamous cell carcinoma; and group 4 three patients with intraepithelial spread of oesophageal cancer to the gastric epithelium. Prognosis was poor, all patients dying except for one in each of groups 3 and 4. The mean survival time was 5·6, 8·6, 14·8 and 18·7 months in groups 1, 2, 3 and 4, respectively. Gastric involvement via metastases to lymph nodes and by intramural metastasis therefore indicates an extremely poor prognosis, while the prognosis in groups 3 and 4 was influenced by the depth of invasion and lymph node metastasis of the oesophageal cancer. Histological examination of tissues from group 4 patients demonstrated that malignant squamous cells proliferated and invaded the gastric epithelial layer, that is, there was intraepithelial spread of the oesophageal cancer.

Oesophageal squamous cell carcinoma is often far advanced at the time of detection and so the prognosis is poor, especially when metastasis has already occurred. The gastric wall is one of the most common areas of such metastasis[1–3]. Oesophageal cancer is sometimes concomitant with gastric carcinoma[4,5]. Once it has been resected, malignant gastric lesions, regardless of their primary or metastatic nature, must be fully assessed. The prognosis for patients who have oesophageal cancer with such metastatic gastric lesions is poor[1] whether they are detected before operation or after histological examination of resected specimens.

The patterns of gastric involvement of oesophageal squamous cell carcinoma include not only intramural metastasis[6], but also involvement via metastatic perigastric lymph nodes, direct invasion, and intraepithelial spread of oesophageal cancer.

This study investigated the clinicopathological and histological characteristics of oesophageal cancer with gastric involvement and each pattern of invasion.

Patients and methods

In the period 1965–1989, 420 patients with oesophageal carcinoma underwent oesophageal resection in this department. After exclusion of 18 patients with adenocarcinoma, 402 patients with primary squamous cell carcinoma of the oesophagus were reviewed. Microscopic sections of the entire resected oesophagus and stomach were made from 0·5 cm wide step-sectioned blocks stained with haematoxylin and eosin. Gastric wall involvement by oesophageal squamous cell carcinoma was identified histologically in 32 patients (8·0 per cent).

These tumours were grouped into the following categories according to the pattern of gastric involvement: group 1, gastric involvement from metastases in perigastric lymph nodes ($n = 6$); group 2, gastric intramural metastasis ($n = 11$); group 3, direct invasion of oesophageal squamous cell carcinoma to the gastric wall ($n = 12$); and group 4, intraepithelial spread of oesophageal cancer into the gastric mucosal epithelium ($n = 3$).

Histopathological criteria for the diagnosis of each group were defined as follows: group 1, definite perigastric lymph node metastases of squamous cell carcinoma continuously invading the gastric wall (*Figure 1*); group 2, foci of squamous cell carcinoma within the gastric wall without any continuity to other lesions (*Figure 2*); group 3, gastric wall involved by direct invasion from the main lesions of squamous cell carcinoma of the oesophagus (*Figure 3*); and group 4, intraepithelial spread along the gastric mucosa of squamous cell carcinoma of the oesophagus (*Figures 4* and *5*).

The clinicopathological characteristics of each group and of the tumours without gastric involvement were investigated.

Results

The clinicopathological characteristics of patients with oesophageal cancer are shown in *Table 1*. There was no difference in the age and sex distribution between patients with and without gastric involvement. Lesions of oesophageal cancer with gastric involvement were more likely to be located in the lower oesophagus in all four groups than those without gastric involvement. Carcinoma in all groups with gastric involvement

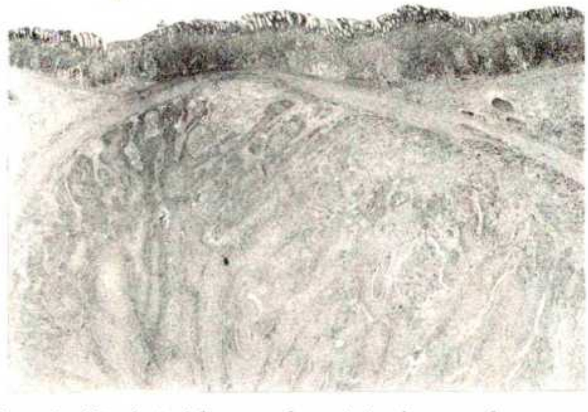

Figure 1 *Histological features of gastric involvement of squamous cell carcinoma via metastatic perigastric lymph nodes (group 1). Squamous cell carcinoma metastasized to the perigastric lymph nodes and invaded from the outer side to the muscularis propria and submucosal layers of the gastric wall. (Haematoxylin and eosin stain, original magnification ×15)*

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also more frequently invaded tissues deeper than the adventitia. Lymph node metastasis was also frequently seen, not only in group 1 but also in other groups with gastric lesions. Thus, oesophageal tumours with gastric involvement are generally more advanced locally and more frequently metastasize to lymph nodes.

Mean survival of the 370 patients without gastric involvement was 4·2 (range 0·1–18·6) years and 1–5-year survival rates in this group were 59·6, 39·2, 30·3, 25·6 and 22·8 per cent respectively.

The prognosis for patients with oesophageal squamous cell carcinoma with gastric involvement was poor, especially for those in groups 1 and 2. All six patients in group 1 died, the mean survival time after operation being 5·6 months. In group

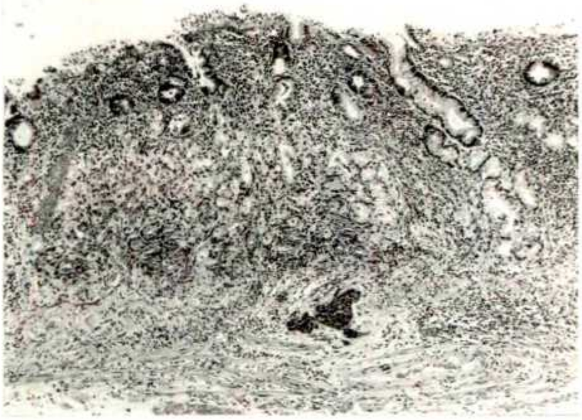

Figure 2 *Histopathology of intramural metastasis of squamous cell carcinoma in the gastric wall (group 2). A tiny focus of metastatic squamous cell carcinoma is present near the muscularis mucosa of the stomach. (Haematoxylin and eosin stain, original magnification × 100)*

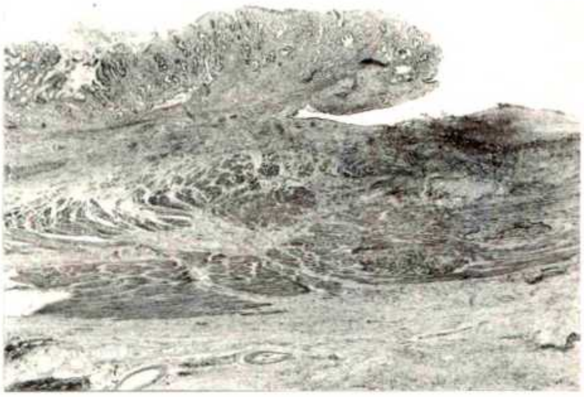

Figure 3 *Direct invasion of oesophageal squamous cell carcinoma into the gastric wall (group 3). (Haematoxylin and eosin stain, original magnification × 20)*

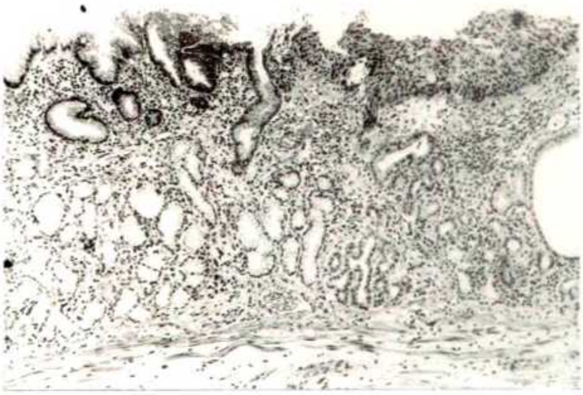

Figure 4 *Intraepithelial squamous cell carcinoma spreading along the gastric epithelial layer (group 4). (Haematoxylin and eosin stain, original magnification × 128)*

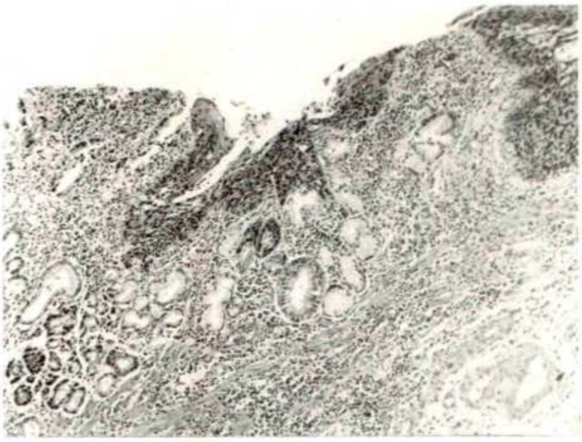

Figure 5 *Intraepithelial spread of oesophageal cancer in a different case from that in* Figure 4. *Squamous cell carcinoma proliferated, replacing the gastric mucosal epithelium. (Haematoxylin and eosin stain, original magnification × 110)*

Table 1 *Clinicopathological characteristics of patients with gastric involvement of oesophageal squamous cell carcinoma and those without a gastric lesion*

	Gastric involvement					No gastric involvement (*n* = 370)
	Group 1 (*n* = 6)	Group 2 (*n* = 11)	Group 3 (*n* = 12)	Group 4 (*n* = 3)	Total (*n* = 32)	
Mean(s.d.) age (years)	66·5(6·4)	61·1(8·7)	66·5(5·9)	61·7(4·9)	64·0(6·5)	62·9(8·8)
Sex ratio (M:F)	5:1	11:0	9:3	3:0	28:4	316:54
Location of tumour						
Upper	1 (17)	0 (0)	0 (0)	0 (0)	1 (3)	50 (13·5)
Middle	2 (33)	6 (55)	1 (8)	1 (33)	10 (31)	241 (65·1)
Lower	3 (50)	5 (45)	11 (92)	2 (67)	21 (66)	79 (21·4)
Depth of invasion						
Within the oesophageal wall	1 (17)	1 (9)	0 (0)	1 (33)	3 (9)	108 (29·2)
Beyond the oesophageal adventitia	5 (83)	10 (91)	12 (100)	2 (67)	29 (91)	262 (70·8)
Lymph node metastasis						
Absent	0 (0)	2 (18)	5 (42)	1 (33)	8 (25)	177 (47·8)
Present	6 (100)	9 (82)	7 (58)	2 (67)	24 (75)	193 (52·2)

Values in parentheses are percentages. For definition of groups see text

Table 2 *Survival of patients with oesophageal cancer involving the gastric wall by direct spread*

Group and patient no.	Depth of invasion	Lymph node metastases	Survival (months)	Outcome
Group 3				
1	Adventitia	Absent	12	Alive
2	Adventitia	Absent	78	Dead
3	Adventitia	Absent	17	Dead
4	Adventitia	Present	17	Dead
5	Adventitia	Present	15	Dead
6	Adventitia	Present	10	Dead
7	Adventitia	Absent	9	Dead
8	Neighbouring organ	Present	6	Dead
9	Neighbouring organ	Present	6	Dead
10	Neighbouring organ	Present	4	Dead
11	Adventitia	Absent	2	Dead
12	Adventitia	Present	2	Dead
Group 4				
1	Muscularis propria	Absent	34	Alive
2	Adventitia	Present	20	Dead
3	Neighbouring organ	Present	2	Dead

For definition of groups see text

2, all 11 patients died, the mean survival time being 8·6 months. All but one patient in each of groups 3 and 4 died. Invasion of the tumour in the surviving patient in group 3 was limited to the adventitia and there was no lymph node metastasis. The tumour in the surviving patient in group 4 was restricted to within the muscularis propria layer with no lymph node metastasis. In these surviving patients, the cancer was relatively less advanced. Survival time of group 3 and 4 patients was related to the depth of invasion and lymph node metastasis (*Table 2*).

Discussion

There have been several reports of gastric metastasis of oesophageal squamous cell carcinoma[1-3]. The prognosis for such patients is extremely poor[1]. Takubo *et al.*[6] demonstrated that the presence of intramural metastasis was an important prognostic factor for patients with oesophageal squamous cell carcinoma, regardless of whether the lesion existed in the oesophagus or gastric wall. However, gastric wall involvement by oesophageal squamous cell carcinoma may be represented by patterns other than intramural metastasis, and data derived from a general investigation of patterns of gastric involvement are few. In this study serial histological investigations were performed and the patterns of gastric involvement by oesophageal cancer separated into four groups, including intramural metastasis and direct invasion from the primary tumour.

Tumours with gastric involvement were generally located in the lower part of the oesophagus; the degree of invasion of such tumours was deeper and lymph node metastasis occurred more frequently than in patients without gastric involvement. Therefore, the prognosis for patients with gastric involvement of oesophageal cancer is poor: in groups 1 and 2 all patients died soon after operation, indicating that gastric involvement by lymph node metastasis or intramural metastasis results in an extremely poor survival rate. On the other hand, the prognosis for patients with gastric involvement by direct invasion (group 3) or intraepithelial spread (group 4) is related to the depth of invasion of the primary lesion and to the presence of lymph node metastasis. Therefore gastric involvement by direct invasion is not itself a significant prognostic factor.

With regard to the occurrence and progression of oesophageal squamous cell carcinoma, it has been suggested that multicentric or field carcinogenesis could be one of the common processes in the development of oesophageal cancer[7-10]. In group 4, intraepithelial squamous cell carcinoma of the oesophagus proliferated and spread along the gastric mucosal epithelial layer (*Figures 4* and *5*). This was histological evidence of intraepithelial spread of oesophageal squamous cell carcinoma, because the carcinoma in the gastric mucosa appeared to represent continuous spread from the primary tumour to the gastric mucosa along the gastric mucosal epithelial layer, rather than the occurrence of intraepithelial squamous cell carcinoma in the gastric mucosa. In these patients, intraepithelial spread of squamous cell carcinoma appeared to be the mode of progression of oesophageal cancer, rather than a field change.

In conclusion, oesophageal tumours that involve the gastric wall or epithelium by direct spread appear to have a similar prognosis to other oesophageal tumours, but gastric involvement by metastases indicates a poor prognosis.

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Case report

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Gastrobronchial fistula owing to non-malignant causes

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Gastrobronchial fistula owing to non-malignant conditions is rare. The most common causes are subphrenic abscess, trauma and previous gastro-oesophageal surgery. In this paper we report our experience with three patients seen at Westmead Hospital over the past 10 years. All cases were managed by the senior author (I.O.O.).

Case reports

Patient 1

A 58-year-old woman was admitted with dysphagia following a Nissen fundoplication at another hospital 3 years previously. This procedure had been complicated by oesophageal rupture and since then she had been troubled by chest infections, dysphagia and occasional postprandial coughing. She had been admitted elsewhere for treatment of pneumonia on a number of occasions. Physical examination was unremarkable except for decreased air entry at the base of the left lung.

A chest radiograph showed collapse of the left lower lobe with a subdiaphragmatic air–fluid level. A barium meal showed communication of the gastric fundus via a left subphrenic cavity with the left lower lobe bronchus with pooling of barium in the left lower lobe. Gastroscopy revealed an inflammatory stricture at 30 cm and bronchoscopy showed markedly inflamed lower lobe bronchi. All biopsies were negative for malignancy.

After a period of nutritional supplementation, left thoracotomy and laparotomy were performed. A collection of pus was found in the left pleural cavity. This collection communicated with a left subphrenic collection. There was a small perforation of the gastro-oesophageal junction but no definite perforation of the lung or bronchus could be seen. A distal oesophagectomy, proximal gastrectomy, pyloroplasty and feeding gastrostomy were performed and gastrointestinal continuity restored with a transverse colon interposition. Histopathological examination confirmed severe oesophagitis with no evidence of malignancy. She was discharged home 3 weeks after operation and remains well 18 months later.

Patient 2

A 72-year-old man was admitted with a 10-year history of gastro-oesophageal reflux and dysphagia. He had suffered from frequent chest infections and a postprandial cough. Gastroscopy revealed an extensive hiatus hernia with an inflammatory stricture at 25 cm. Bronchoscopy showed gastric contents in the left main bronchus. All biopsies were negative for malignancy.

A right thoracotomy demonstrated a large gastro-oesophageal ulcer eroding into the left main bronchus. An oesophagectomy, proximal gastrectomy and cervical oesophagostomy were performed and the defect in the left main bronchus repaired with a vascularized intercostal muscle patch.

Histopathological examination confirmed severe inflammation of the oesophagus with extensive intestinal metaplasia consistent with Barrett's oesophagus but there was no evidence of malignancy. Six months later the patient underwent oesophageal reconstruction with colon interposition. In the year after operation, he suffered progressive deterioration in his respiratory state and died from pneumonia 6 years after his initial presentation.

Patient 3

A 68-year-old woman was admitted with a history of haematemesis and melaena. After resuscitation, gastroscopy showed a large gastro-oesophageal ulcer and extensive inflammation. All biopsies were negative for malignancy. Twelve days after admission she developed septic shock with large bilateral pleural effusions and drainage of gastric contents via the chest drains. Gastrografin (Schering, Sydney, Australia) swallow showed a large paraoesophageal hernia (*Figure 1*) with leakage of contrast into the left lower lobe bronchus (*Figure 2*).

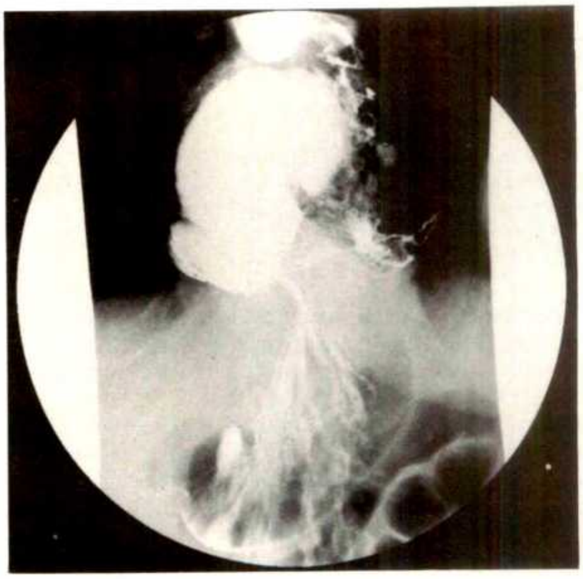

Figure 1 *Gastrografin swallow in patient 3 showing a large paraoesophageal hernia*

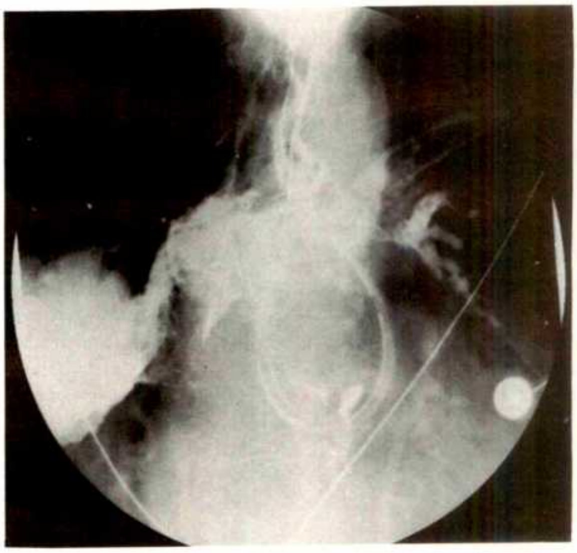

Figure 2 *Gastrografin swallow in patient 3 showing leakage of contrast into the left lower lobe bronchus*

A right thoracotomy revealed a hugh paraoesophageal hernia with a 5-cm perforation at the gastro-oesophageal junction communicating with the left lower lobe bronchus. Distal oesophagectomy, proximal gastrectomy, cervical oesophagostomy and feeding gastrostomy were performed. The defect in the bronchus was not searched for but was left within the inflammatory mass. The patient had a stormy postoperative course which included a decortication of the left lung for an empyema, but was discharged 3 months after admission. She is currently awaiting reconstruction of her gastrointestinal tract.

Discussion

Benign gastrobronchial fistulae are rare. In an extensive review of the English literature, we have been able to identify only 16 cases$^{1-5}$. The causes of these fistulae, including our own, are summarized in *Table 1*.

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Table 1 *Causes of 19 cases of gastrobronchial fistula in a survey of the literature, including the three present cases*

Cause	*n*
Trauma	4
Gastro-oesophageal surgery	2
After Nissen fundoplication	4
Subphrenic abscess	3
Gastric ulcer	3
Tuberculosis	1
Paraoesophageal hernia	1
Ectopic gastric pancreatic tissue	1

Full references available on request

Subphrenic sepsis has been implicated in the aetiology of gastrobronchial fistula and was certainly a contributing factor in our first case. Infection may spread by lymphatic flow from below to above the diaphragm.

Gastrobronchial fistula following Nissen fundoplication has been reported three times before, but each of these cases occurred secondary to gastric ulceration after intrathoracic fundoplication. Gastric ulceration occurs in 3–5 per cent of patients after fundoplication[6], and theories as to the aetiology of these ulcers include gastric hypersecretion secondary to gastric distension[6], inadvertent division of the vagal fibres[7], and ischaemic ulceration from devascularization of the stomach[8]. To our knowledge there is only one report of gastric fistulation into another organ after Nissen fundoplication, which appeared to be related to suture reaction rather than gastric ulceration[9].

The second of our cases was related to Barrett's oesophagus and it appears that these patients have a particularly aggressive form of reflux oesophagitis with a 90 per cent prevalence of a mechanically defective sphincter and a 44 per cent prevalence of gastric hypersecretion[10]. As the disease progresses, there is loss of oesophageal contractility and this predisposes further to giant ulcer formation with bleeding or erosion.

Paraoesophageal hernias constitute less than 5 per cent of all hiatal hernias, but become incarcerated in at least 30 per cent of cases[11]. Once incarceration occurs, bleeding and perforation are likely and the mortality rate is high. We believe that all of these hernias should be repaired and that there is no place for conservative therapy.

These patients are often acutely ill with intrathoracic sepsis. Primary surgical management is by oesophagectomy with proximal gastrectomy, gastrostomy and cervical oesophagostomy. If a large bronchial defect is present, this must be closed, usually with a vascularized intercostal muscle patch. Where it is impossible to identify the fistula track in a large inflammatory mass, it is probably best to isolate the area with a distal oesophagogastrectomy and cervical oesophagostomy, and leave the fistula to close spontaneously.

In conclusion, gastrobronchial fistulae owing to benign causes are rare but should be suspected in patients with recurrent lower lobe pneumonia who have a paraoesophageal hernia or who have had previous gastro-oesophageal surgery. With prompt treatment, good results can be expected.

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Attitudes and experiences of human immunodeficiency virus-positive patients to surgery and surgeons

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The issues regarding screening and identification of patients at risk for human immunodeficiency virus (HIV) infection before surgery continue to be discussed, and there is a need for information regarding attitudes of both surgeons and patients to this issue. A population of HIV-positive patients attending a genitourinary medicine clinic were given an anonymous questionnaire to review their experiences of attending for operation. Of 174 patients who replied, 52 had undergone a total of 65 procedures. In all but three of the operations, the HIV status was made known to the surgeon.

A statement from the Royal College of Surgeons of Edinburgh suggesting that all patients presenting as an emergency be screened for human immunodeficiency virus (HIV) infection before surgery has raised important issues regarding such operations[1]. Surveys have been published[2,3] examining attitudes of surgeons and operating theatre staff towards infected patients, but there has to date been no published account of patients' attitudes. HIV-positive patients are concerned about the possibility of discrimination, loss of confidentiality, and delay or cancellation of surgical procedures should their HIV status be disclosed. In a recent survey of attitudes of general surgeons to HIV in England and Wales[3] some surgeons stated: 'If I know they are HIV positive, I will not operate on them'. Some also stated: 'Surgery should be for life-saving conditions only'. Although this was not the opinion of the majority of surgeons, if such discrimination is perceived by the affected patient group they may become less likely to disclose their risk behaviour or HIV status, perhaps putting the surgeon and other healthcare workers at risk. This survey sets out to examine a group of HIV-positive patients attending a genitourinary medicine clinic.

Patients and methods

The intention was to establish: (1) whether patients would be prepared to disclose their HIV status if attending for surgery; (2) what surgical procedures had been performed on them and whether the surgeon was aware of their HIV diagnosis at the time; and (3) what the patients' attitudes were towards disclosing their HIV status to dentists.

A questionnaire was handed only to patients known to be HIV positive at the end of a consultation with their physician. The questionnaires were anonymous and patients had the option of not completing them. Copies of the full questionnaire can be obtained from the authors.

Results

Of 176 questionnaires handed to patients with HIV in the clinic, only two were returned unanswered. There were 173 male respondents and one woman. The mean age of the patients was 34 years 8 months, and the mean duration of known HIV infection was 31·1 months. Of 174 patients replying to the survey, 52 (30 per cent) had undergone a total of 65 operations since becoming aware of their HIV status, 11 as an emergency, the rest as planned procedures (*Table 1*).

For all but three of the procedures, the surgeon was aware of the HIV status of the patient. The information regarding HIV status was obtained in 33 cases (51 per cent) by the surgeon being informed by another doctor. In 25 cases (38 per cent) the patient volunteered the information. In two cases (3 per cent) an HIV test was performed as preoperative screening. In the last two cases the surgeon asked for the information.

In the three instances in which the surgeon was unaware of the HIV diagnosis, the procedures were abscess drainage, tooth extraction and repair of laceration. The reasons cited by the patients for not informing the surgeons were: the surgeon did not ask; the surgeon did not ask and the patient felt that reasonable precautions were being taken; the patient was worried about delay or cancellation of the procedure. Additional comments were made by six patients: 'An exploratory operation was put off on the grounds of HIV infection'; 'A planned circumcision was changed to a dorsal slit on the grounds of HIV infection and the anaesthetist refused to touch me'; 'A surgeon in Plymouth refused to operate on me so I came to London'; 'I have been recommended to have wisdom teeth removal but have been unable to find a dentist who will do this on the grounds of my HIV infection'; 'A London teaching hospital refused to operate on me unless I had a test so I transferred to another hospital'; and 'My old dentist refused to treat me once he was aware of my HIV status'.

Of the 174 patients, 137 saw their dentist annually or more frequently. However, 48 (35 per cent) of these 137 patients had not informed their dentist of their HIV status. When dentists were aware of HIV status this information was volunteered by the patient in 87 (98 per cent) of 89 cases. In only two instances did the dentist ask for information. When the dentist was unaware of the HIV status of the patient, some patients argued: 'He knows my HIV status' or 'She wears gloves'.

Table 1 *Procedures performed on patients with known human immunodeficiency virus infection*

Procedure	Planned	Emergency
Bronchoscopy/lung biopsy	9	1
Perianal surgery	11	1
Urological surgery	2	1
Skin biopsy	5	0
Lymph node biopsy	8	0
Arthroscopy/other orthopaedic procedure	2	2
Abscess drainage	1	4
Splenectomy	2	0
Abortion	1	0
Insertion of Hickman line	3	0
Tooth extraction	3	0
Other minor procedures	7	2
Total	54	11

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Discussion

This is the first study to examine the attitudes of HIV-positive patients to surgery. The surgeon was aware of the HIV status of most patients undergoing operation in this hospital. In the three instances in which the surgeon was unaware of the HIV status the respondents implied that they would have volunteered this information had they been asked. This is particularly encouraging, given that discrimination is perceived to exist judging by the patients' additional comments. Although anxiety in surgeons regarding HIV-positive patients is understandable, there is little evidence to suggest a significant risk of infection[4–7]. Although these initial findings suggest that patients are willing to inform their surgeon of their HIV status, we are concerned at the 35 per cent who regularly attend a dentist and do not disclose their seropositivity. It is also important to remember that the prevalence of the infection in the community is increasing and that many infected persons may not consider themselves at risk or know their HIV status[8,9].

There is a need to create a climate in which patients who do know their HIV status will be happy to volunteer this information without fear of discrimination. Such information should be welcomed by the surgeon as it gives an opportunity for reassessing management and in some cases surgery may even be avoided[10,11]. Furthermore, it gives an opportunity for making safety provisions for the surgical team and other healthcare workers[6].

This study shows that, at present, most patients when confronted by surgeons are willing to disclose their seropositivity. Exceptions to this may arise when the patient is apprehensive of possible discrimination. Refusal to treat will only force patients to seek help elsewhere and may confer unnecessary risk on surgical colleagues through patients withholding their HIV status.

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Proliferation indices of invasive breast carcinomas after *in vivo* 5-bromo-2′-deoxyuridine labelling: a flow cytometric study of 75 tumours

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In vivo *labelling of human breast tumours with 5-bromo-2′-deoxyuridine and analysis of proliferation by multiparameter flow cytometry is a new tool by which the labelling index, S phase duration* (T_s) *and potential doubling time* (T_{pot}) *of the tumour can be estimated. Tumour specimens from 75 patients with invasive breast carcinoma were studied. Six tumours could not be analysed, and the* T_s *and* T_{pot} *values could not be calculated for a further 18. The median labelling index* ($n = 69$) *was 4·2 per cent. The median* T_s ($n = 51$) *was 8·7 h and the median* T_{pot} ($n = 51$) *was 8·2 days. The median intra-assay coefficient of variation for determination of the labelling index was 0·29 in five tumours. There were no significant differences in the total labelling index,* T_s *or* T_{pot} *when patients were stratified according to lymph node status, tumour size, tumour grade or menopausal status.*

The factors determining the behaviour and potential for successful treatment of invasive breast cancer are not fully understood. The rate of cell proliferation may be one such factor. The presence of involved lymph nodes is a clear indication of metastatic potential in the primary tumour, and lymph node metastases are the best prognostic index[1]. Tumour size, grade and receptor status provide useful information but cannot accurately predict the outcome or optimal treatment.

Labelling indices of breast tumours have been calculated by *in vitro* tritiated thymidine labelling[2–4] and using *in vitro* 5-bromo-2′-deoxyuridine (BrdU) labelling[5,6] (*Table 1*). Gentili *et al.*[7] found that the median breast tumour thymidine labelling index was significantly higher in premenopausal than in postmenopausal patients, but similar in node-negative and node-positive tumours. A low *in vitro* thymidine labelling index may be a predictor of prolonged disease-free survival in patients with negative nodes[3,8,9].

Monoparameter flow cytometric analysis of DNA content is an established technique and the S phase fraction (SPF) is an index of tumour proliferation which can be estimated from flow cytometry histograms[10–13]. It is a static, indirect index which gives no measurement of the rate of cell proliferation. Aneuploidy and a high SPF may correlate with the biological aggressiveness of breast carcinomas[4,9,14–17].

BrdU is a non-radioactive alternative to tritiated thymidine for *in vivo* pulse labelling studies in patients with malignancy. Measurement of the labelling index by BrdU histochemistry underutilizes the available information. Multiparameter flow cytometry (MFCM) and *in vivo* labelling with BrdU allows the DNA index, the SPF, the total and aneuploid (where relevant) labelling indices and two dynamic indices, the S phase duration (T_s) and the potential doubling time (T_{pot}), to be calculated from single samples[18–21].

This study measured the cell kinetics of breast carcinomas after *in vivo* labelling with BrdU, and compared results with lymph node status, tumour size and grade.

Patients and methods

Seventy-five women with a definitive diagnosis of breast cancer consented to receive a single intravenous dose of 250 mg BrdU administered over 30 s in 10 ml saline, between 1·75 and 10·0 h before surgery. No toxicity was associated with this procedure. After tumour excision, biopsies were immediately excised, fixed in 70 per cent ethanol and stored cold for later flow cytometry.

Disaggregation

Tumours were finely minced and incubated in 0·3 mg/ml porcine pepsin (Sigma, Poole, UK) in 8 ml 0·1 M HCl at 37°C for 30 min; 150 µl of Triton X-100 was added to digests with high fat content. The suspension was filtered through a 35-µm mesh and washed. Nuclei were denatured in 2 M HCl for 8 min at room temperature and then washed in fresh phosphate-buffered saline (PBS). The concentration of nuclei was adjusted to approximately 2 × 10^6 per ml.

Antibody labelling

Nuclei were resuspended in a solution of 0·5 ml 0·5 per cent Tween 20 and 0·5 per cent normal goat serum (NGS; Sigma) in PBS, and 25 µl anti-BrdU monoclonal antibody supernatant (ICRF, Sutton, UK) was added. Nuclei were washed and incubated in the 0·5 per cent Tween 20–NGS–PBS solution and 35 µl goat antirat antibody conjugated to fluorescein for 1 h at room temperature. Nuclei were then washed twice in PBS and resuspended in 3 ml PBS containing 10 µg/ml propidium iodide (PI, Sigma).

Flow cytometry

Analysis was performed on an Ortho Systems 50-H cytofluorograph (Becton–Dickinson, Oxford, UK). Excitation was at 488 nm from a 5-W argon ion laser operating at 200 mW. Green light (fluorescein emission) indicating BrdU labelling was collected at 510–560 nm. Red fluorescence (PI emission) indicating DNA content was collected above 620 nm. Data for 7000–15 000 nuclei were collected in list mode. The data were gated to exclude multiple nuclei (*Figure 1*).

Table 1 *Selected reports of the labelling index of human breast tumours as measured by different methods*

Method	Labelling index (%)	*n*	Reference
TLI *in vitro*	2·4 (0·1–9·7)	50	2
TLI *in vitro*			7
Premenopausal	4·2	342	
Postmenopausal	1·8	199	
TLI *in vitro*	1·0 (0·06–16·8)	128	9
TLI *in vitro*	6·6 (0·05–35·6)	278	3
TLI *in vitro*	7·5 (0·3–23·1)	142	4
TLI *in vitro*	7·3 (0·3–20·0)	30	24
SPF/FCM	n.a. (1·1–24·4)	168	4
SPF/FCM	n.a. (0·7–37·4)	104	14
BrdU *in vitro*	9·3 (1·6–23·4)	20	5

Values are mean (range). TLI, thymidine labelling index; SPF/FCM, flow cytometric S phase fraction; BrdU, 5-bromo-2′-deoxyuridine; n.a., data not available

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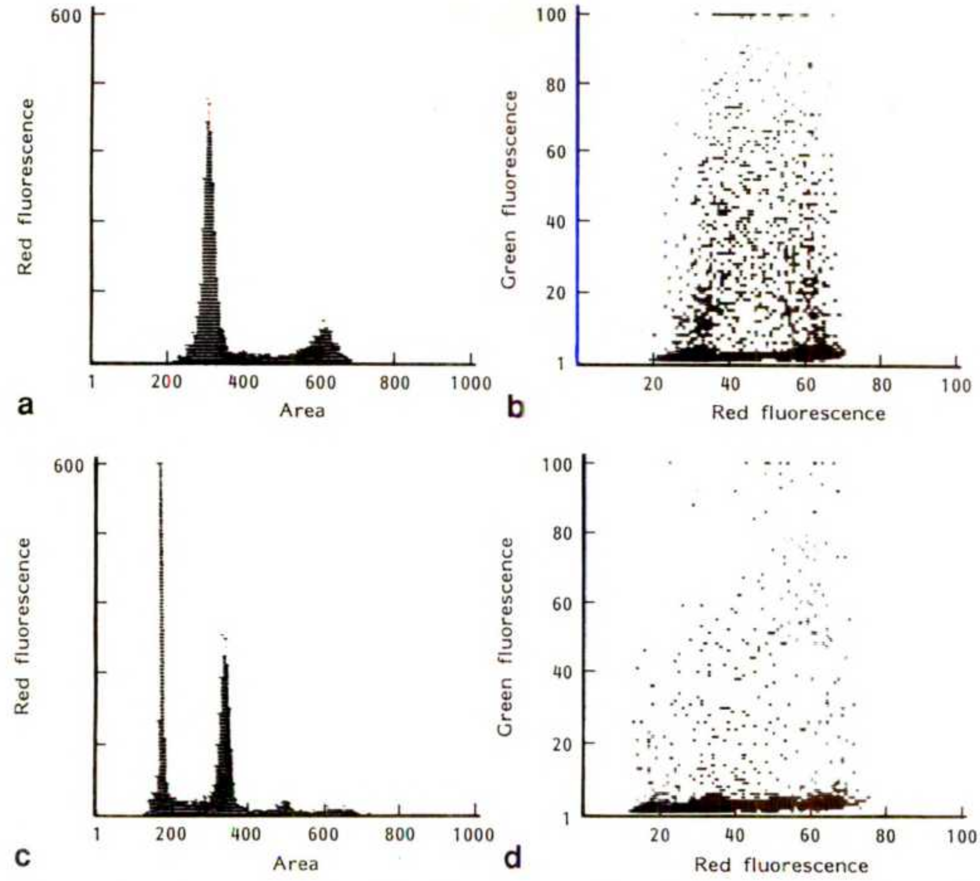

Figure 1 *Representative histograms of* **a, b** *diploid and* **c, d** *aneuploid breast carcinomas labelled with 5-bromo-2'-deoxyuridine (BrdU).* **a, c** *DNA profiles.* **b, d** *BrdU content (y axis) in relation to DNA content (x axis). Each point represents the fluorescent events associated with one nucleus*

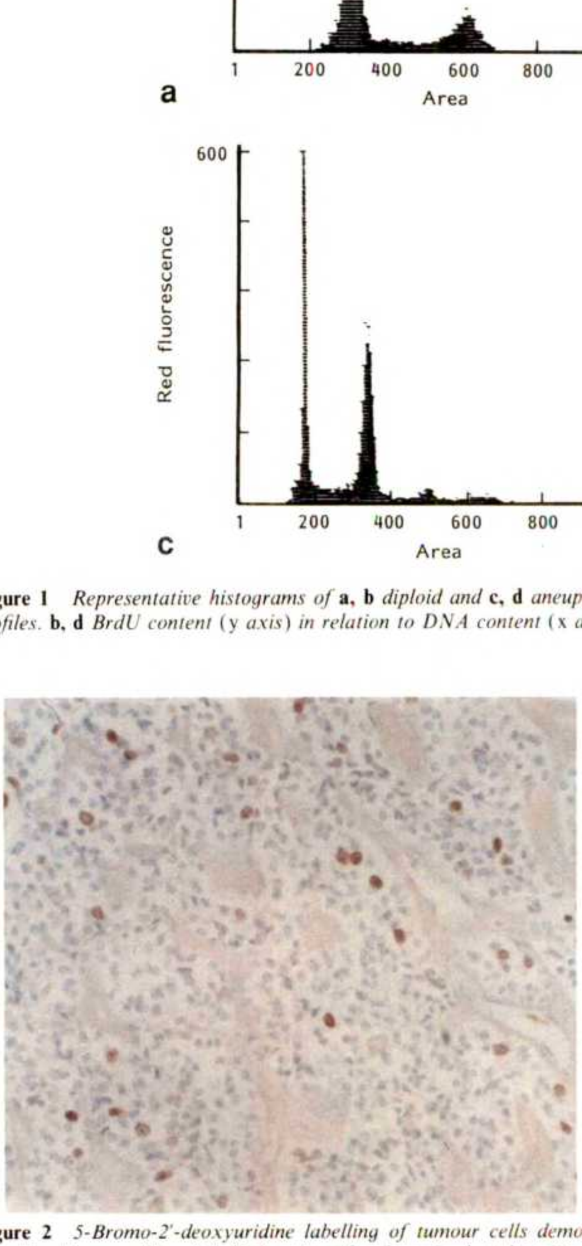

Figure 2 *5-Bromo-2'-deoxyuridine labelling of tumour cells demonstrated in this peroxidase-labelled section of an invasive ductal carcinoma (original magnification × 25)*

Data analysis

Analysis was performed by a method previously described[21]. The potential doubling time, T_{pot}, is related to the total labelling index (LI) and the S phase duration by the formula

$$T_{pot} = (T_s/\text{LI}) \times 0{\cdot}8$$

The coefficient of variation (c.v.) of the assay was assessed by finely mincing and mixing large biopsies (0·5 cm^3) from each of five tumours and dividing each tumour residue into six fractions, which were then prepared and analysed in identical fashion. The c.v. of intratumour heterogeneity was assessed in eight large tumours from which at least four biopsies from widely dispersed sites were analysed. Some specimens were unsuitable for measurement of T_s because the G1, S and G2/M phases of the DNA histogram were ill-defined. In these cases the correction to account for the number of daughter cells in the G1 phase resulting from division of BrdU-labelled cells could not be made. This produces a slight overestimation of the true labelling index in these tumours, a situation akin to the labelling index derived from static counting in histochemical or autoradiographic sections, where daughter cells in the G1 phase cannot be distinguished from other labelled cells. A c.v. of up to 10 per cent in the G1 peak width was accepted because of the additional DNA denaturation stage using 2 M HCl in this procedure.

Parametric and non-parametric analyses of the data were made by Student's *t* test (two-sample analysis of variation) and the Mann–Whitney *U* test, respectively (Statgraphics software; STSC, Rockville, Maryland, USA).

Formalin-fixed tissue sections were analysed. Tumour size was measured before the tumours were embedded in wax. Tumours were graded according to the criteria of Bloom and Richardson[22]. A small number of formalin-fixed wax-embedded 5-μm sections of tumours were also stained by a standard avidin–biotin–peroxidase technique[23] (*Figure 2*).

Results

Seventy-five patients with invasive carcinoma of the breast were studied. There were three lobular carcinomas, one tubular and one primary squamous carcinoma. The remainder were ductal carcinomas. The age range was 39–80 years. Patients underwent simple mastectomy with axillary clearance ($n = 59$), wide local excision with axillary clearance ($n = 15$) or wide local excision alone ($n = 1$). The median time between BrdU injection and labelling was 4·0 (range 1·75–10·0) h.

Six primary tumours (8 per cent) failed to yield analysable data on flow cytometric analysis on at least two occasions using different biopsies from within the tumour block. Of the 69 analysable tumours, 38 patients had positive nodes and 30 negative nodes. The node status of one tumour was not known. There were 23 T_1, 36 T_2 and ten T_3 tumours. Twelve patients

Table 2 *Intra-assay coefficients of variation of the kinetic data from five diploid tumours*

	Coefficient of variation		
Specimen	LI	T_s	T_{pot}
B15	0·35		
B17	0·29	0·12	0·45
B22	0·73	0·21	0·41
B42	0·07	0·15	0·18
B49	0·06	0·15	0·19

Six aliquots of nuclei were analysed from one region of each tumour. LI, labelling index; T_s, S phase duration; T_{pot}, potential doubling time

Table 3 *Kinetic data for primary breast carcinomas and when stratified by node status*

Specimen	n	
All tumours		
Total LI (%)	69	4·2 (0·6–15·4)
T_s (h)	51	8·7 (2·7–22·2)
T_{pot} (days)	51	8·2 (1·8–47·5)
Node-negative tumours		
Total LI (%)	30	4·6 (1·2–15·4)
T_s (h)	22	8·7 (2·7–22·2)
T_{pot} (days)	22	5·8 (1·8–40·6)
Node-positive tumours		
Total LI (%)	38	4·0 (0·6–15·0)
T_s (h)	28	9·0 (3·3–21·6)
T_{pot} (days)	28	8·6 (3·0–47·5)

Values are median (range). LI, labelling index; T_s, S phase duration; T_{pot}, potential doubling time. The node status of one tumour (total LI 2·5 per cent, T_s 9·4 h, T_{pot} 10·4 days) was not known

were premenopausal or perimenopausal and 57 were postmenopausal.

Ploidy data

Eleven tumours with demonstrable uptake of BrdU yielded histograms from which aneuploidy could not be excluded with confidence. Of the 58 tumours with a well defined DNA profile, 29 were diploid and 29 were aneuploid. Nine of 24 node-negative tumours were aneuploid (four profiles were ill-defined) and 19 of 33 node-positive tumours were aneuploid (six profiles were ill-defined). The single tumour of unknown node status was aneuploid.

Intra-assay variation. Six specimens taken from one region of each of five tumours were prepared and analysed in identical fashion. The coefficients of variation of the resulting data are shown in *Table 2*. All tumours had a low labelling index. Insufficient tumour material was available to repeat this experiment on tumours with a high labelling index.

Proliferation parameters

The data are given in *Table 3*. The aneuploid labelling index was used to estimate T_{pot} in seven node-negative and 17 node-positive tumours. A total labelling index only was measured in 18 specimens which were unsuitable for measurement of T_s because the G1, S and G2/M phases of the DNA histogram were ill-defined.

Node status. There were no significant differences in the total or aneuploid labelling indices, T_s or T_{pot} between node-negative and node-positive tumours (*Table 3*).

Tumour size. There was no significant difference between the labelling index and the maximum tumour diameter or T stage. The median labelling index of T_1 tumours ($n = 23$) was 4·3 per cent, of T_2 tumours ($n = 36$) 4·0 per cent and of T_3 tumours ($n = 10$) 4·1 per cent (*Figure 3*).

Tumour grade. In the 57 ductal tumours for which grading data were available (nine G_1, 19 G_2 and 29 G_3), there was no correlation between total labelling index or T_{pot} and tumour grade (*Figure 4*).

Menopausal status. There was no significant difference between the total labelling index, T_s or T_{pot} values of the premenopausal ($n = 12$) and postmenopausal ($n = 57$) women.

Intratumour variation

Coefficients of variation of the labelling index were calculated in eight tumours where at least four separate regions could be analysed. The median intra-assay c.v. of the LI was 0·29 and the median intratumour c.v. of heterogeneity was 0·35

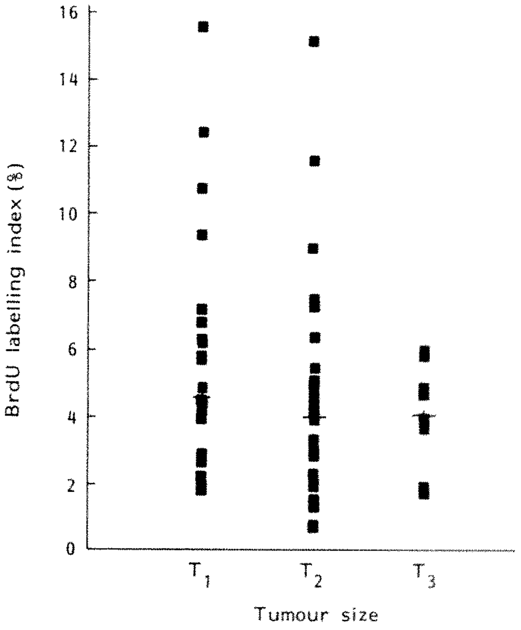

Figure 3 *Correlation between tumour size and 5-bromo-2′-deoxyuridine (BrdU) labelling index (see text). +, Median value*

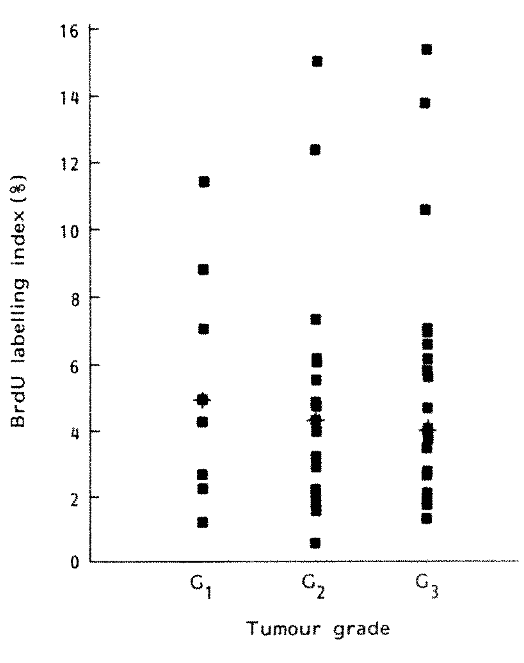

Figure 4 *Correlation between tumour grade and 5-bromo-2′-deoxyuridine (BrdU) labelling index (see text). +, Median value*

(difference not significant, Student's *t* test). It was not possible in this series to distinguish heterogeneity in proliferation data from variability in the assay, particularly in tumours with a low labelling index.

Discussion

Current proliferation indices are unsatisfactory. *In vitro* assessments of the labelling index of human tumours using tritiated thymidine are time-consuming. Monoparametric flow cytometry, although producing more rapid analyses, is subject to a number of interpretational problems. The flow cytometric SPF gives no measure of the rate of cell proliferation. SPF data are significantly affected by the quality of DNA histograms, by preparation artefacts and by overlapping diploid and aneuploid populations in histograms derived from aneuploid tumours. Diploid tumours may be interpreted as aneuploid because of artefacts. Up to 40 per cent of tumours in large series may fail to yield acceptable DNA profiles[15].

There are methodological problems with our data, as discussed below.

Specimen selection

There was a deliberate selection bias against tumours $<1{\cdot}5$ cm in diameter because fewer small tumours have a definitive preoperative diagnosis and provide sufficient material.

Disaggregation

Experience with colorectal tumours[19] indicated that 70 per cent ethanol may be a less disruptive fixative for flow analysis than formalin. Disaggregation of breast tumours was variable. Some tumours were very sensitive to standard disaggregation methods and excessive DNA disruption gave very broad G1 and G2 peaks after disruption of the connective tissue matrix. Better results may be achieved in future using freshly excised tissue[24].

Limitations of multiparameter flow cytometric analysis

Estimation of T_s assumes: that the bolus of BrdU is handled as a true pulse label, and not stored for gradual incorporation into S phase DNA; that incorporation of BrdU with S phase progression is linear and stoichiometric; and that the cell cycle model on which the calculations are based closely approximates to real kinetic events *in vivo*.

No satisfactory technique exists for distinguishing the diploid G1 tumour cells from stromal cells in the G1 peak, but the numbers of the various cell types can be established by quantitative histochemistry. Where aneuploid tumours were analysed by flow cytometry, gating was performed on the aneuploid G1, S and G2 populations to calculate the aneuploid labelling index, T_s and T_{pot}. This region more accurately reflects tumour proliferation because it excludes stromal cells in the diploid G1 population. The overlap of the aneuploid G1 and S phases with the diploid S and G2 phases adversely affects the data, particularly where a large diploid tumour population coexists.

In vitro data obtained using thymidine or BrdU labelling are equivalent and correlate with the SPF measured by flow cytometry. The BrdU/MFCM technique is a practical method with which to measure labelling of carcinomas of the breast. It analyses large numbers of nuclei and reduces the sampling errors inherent in manual cytometry. Results were comparable to those obtained by thymidine labelling *in vitro* (*Table 1*). The major advantage of using the *in vivo* BrdU/MFCM technique is the dynamic (T_s and T_{pot}) data obtainable. In animal tumour studies, a significant S phase movement of labelled cells can be detected as little as 1 h after injection of BrdU[21]. The T_s values for this series of tumours are comparable to those calculated for other human tumours by this technique.

The T_s and the labelling index are independent variables from which the T_{pot} is calculated. There appears to be considerable heterogeneity in proliferation both within and between breast carcinomas. For tumours with a labelling index of $<1{\cdot}0$ per cent, the counting of 100000 events would give a more accurate T_s estimation.

The T_{pot} measurement is calculated only at one time point on the tumour growth curve. The proportion of proliferating cells and the cell loss factor are likely to change with time and tumour size. Factors such as cellular hypoxia and altered immune response may be important. No relationship between tumour size and proliferation parameters was seen.

The increase in counting efficiency afforded by flow cytometry facilitates the study of tumour heterogeneity[25]. Caution should be used in deducing the proliferative status of a tumour from a single biopsy or tissue section. No ideal method of measurement of static and dynamic proliferation indices is yet available, and proliferation parameters are an incomplete description of tumour aggressiveness. Node status remains the best single index of prognosis.

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Announcement

Eurochirurgie/Eurosurgery

The idea of a European surgical organization originated in Strasbourg in 1988.

Eurochirurgie/Eurosurgery represents a focal point at which surgeons from all countries of Europe can exchange information and views and discuss common problems. Drawing its membership from national surgical associations, and working in harmony with them, Eurochirurgie does not itself constitute a new association or society. Rather, it is an organization whose prime purpose is to promote an annual or biennial European Surgical Congress, and to maintain continuity from year to year. The Permanent Secretariat is in Paris.

Eurochirurgie is multidisciplinary, and includes all surgical specialties. It is multipurpose, and is concerned with clinical practice and scientific research, with training, and with professional organization. Its activities comprise: symposia and workshops, free and invited paper sessions, posters, videos, trade exhibitions and fora for discussion of the challenges which face surgeons in the context of European unity.

The first Eurochirurgie Meeting took place in Paris in October 1990 under the Presidency of a Belgian surgeon and attracted 4500 delegates from all over Europe. Plans for the next Congress, in Brussels in June 1992 (with a British President), are well in hand and include sessions devoted to continuing medical education.

The following year, 1993, will see the Congress in the Royal Festival Hall in London, and meetings thereafter are planned for Berlin, Barcelona and Rome. The meeting is not confined to surgeons but is open to all concerned with care of the surgical patient including nurses, physiotherapists, orthotists and health administrators.

It is the nearest European parallel to the annual American College of Surgeons Meeting in the USA, and is an important development in European cooperative healthcare.

Further information about Eurosurgery can be obtained from: Department of External Affairs, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK.

Adrian Marston
Vice-President
The Royal College of Surgeons of England

Br. J. Surg. 1992, Vol. 79, April, 340–341

Shrinkage of the below-knee stump in leprosy

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The long-term progress of below-knee stumps was studied in 65 leprotic amputees. Thirty-seven patients underwent amputation with a long posterior flap (LP) and 28 patients with an equal anterior and posterior flap (EF) technique. Mean follow-up was for 6 and 7 years respectively. Shrinkage of the soft tissue and retraction of the posterior calf muscles caused the posterior skin flap of the stump to rotate posteriorly in all cases, with a mean 26° of rotation in LP stumps and 42° of rotation in EF stumps. The LP stumps remained thicker, with soft tissue padding at the bony ends, and had fewer stump complications than the EF stumps.

Leprosy is one of the major causes of neuropathic ulcers and neuroarthropathy of the foot. When it is complicated either by malignant change in the long-standing neuropathic ulcers or by infection spreading to the underlying tarsal bones, a below-knee amputation is often indicated. As there are no ischaemic or diabetic complications and there is no specific recommended technique, most surgeons prefer the conventional procedure with equal anterior and posterior flaps (EF). In patients with neuroarthropathy of the foot, the muscles innervated by the peroneal nerve are usually severely paralysed[1]. When these patients undergo below-knee amputation, the soft tissue padding of the bony stump is provided mainly by the posterior calf muscles. Later, these muscles usually shrink and retract proximally, causing posterior migration of the posterior skin flap, while the thinner anterior flap rotates to cover and support the end of the bone. This process often causes skin breakage or painful bursitis at the end of the stump after long-term use of a prosthesis. We observed a different incidence of such complications when using a long posterior flap (LP) or the conventional EF technique. The long-term results of these two techniques were therefore studied (*Figure 1*).

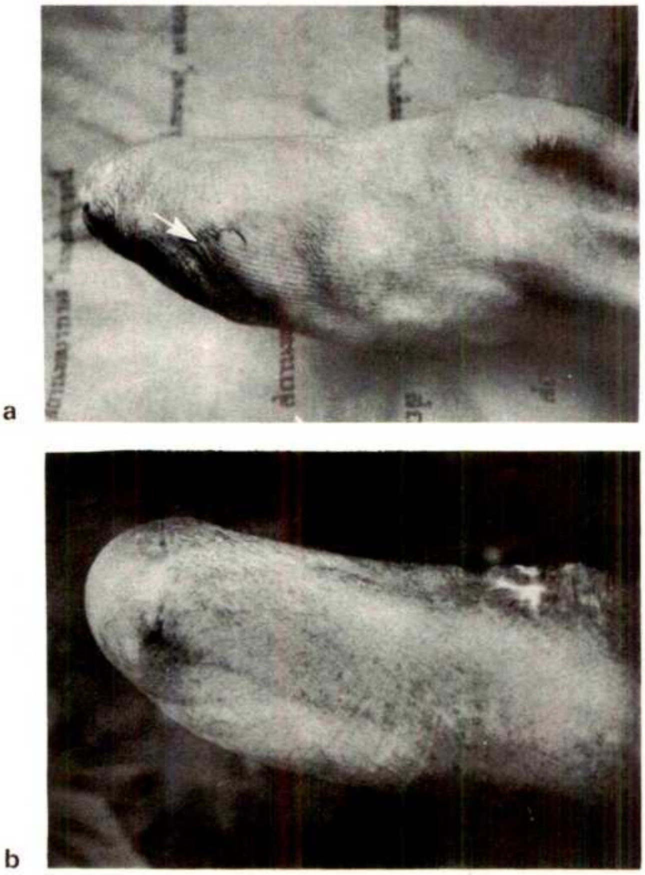

Figure 1 **a** *Below-knee stump in a leprotic patient 7 years after amputation using equal anterior and posterior flaps. Note proximal retraction of the posterior calf muscles and posterior rotation of the posterior skin flap, as identified by deviation of the surgical scar (arrow).* **b** *Below-knee stump in a leprotic patient 5 years after amputation by the long posterior flap technique. There is no retraction of the skin flaps*

Patients and methods

Between 1976 and 1990, 157 leprotic patients underwent below-knee amputation at Nonsomboon Leprosarium, Khon Kaen. The reason for amputation in almost all cases was malignant change of long-standing neuropathic ulcers of the foot or intractable chronic osteomyelitis of the tarsal bones in a severely deformed foot. At the time of this study, 74 amputees who had undergone amputation more than 2 years previously and who were living in the leprosarium were available for follow-up.

Regarding operative technique, the choice between the EF and LP techniques was based on the surgeon's familiarity with each particular procedure. The level of tibial transection was 12–15 cm distal to the tibial tuberosity. The anterior part of the tibia was bevelled, and the fibula was cut 1 cm short of the tibia. Muscle fixation was achieved by suturing the posterior fascia to the pretibial fascia with interrupted sutures in both techniques. The stumps were covered either with a plaster cast or loosely with soft bandages, according to the surgeon's preference.

Of 74 amputees, nine were excluded from the study. These included two patients in whom stumps healed by secondary intention (and secondary suture), two patients with bilateral amputation and another five with unilateral amputation who never used a prosthesis. The remaining 65 amputees were studied for the range of knee flexion, flap migration (*Figure 2*), condition of the stump (including skin integrity) and radiological evaluation of soft tissue thickness at the end of the tibial stump. Student's t test was used for statistical analysis and significance taken at $P < 0{\cdot}05$.

Results

The clinical data are shown in *Table 1*. Flap migration occurred as a result of stump shrinkage in every case but tended to be greater with the EF procedure (42 *versus* 26°, P not significant). The LP technique provided more soft tissue padding (2·8 *versus* 1·2 mm, $P < 0{\cdot}05$) and a more anterior positioning of the suture line even after stump shrinkage. In addition, there was a higher incidence of skin breakdown and painful stump bursitis in patients with EF stumps. There was no limitation of knee flexion in any patient in this study.

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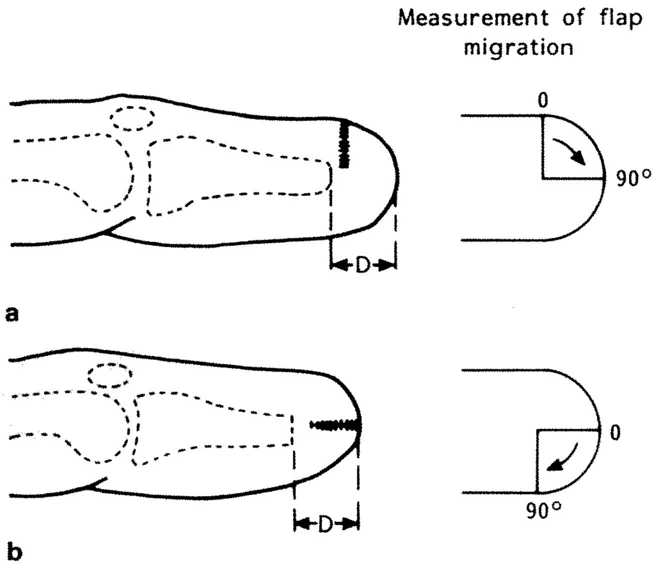

Figure 2 *Diagram showing the method of measuring the thickness of the soft tissue padding (D) at the end of the stump. Radiographs were obtained in lateral projection, and flap migration was determined by the degree of rotation of the surgical scar.* **a** *Long posterior flap and* **b** *equal flap techniques*

Table 1 *Clinical data in 65 patients undergoing below-knee amputation by the equal flap technique or the long posterior flap technique*

	Equal flap technique ($n = 28$)	Long posterior flap technique ($n = 37$)	P*
Mean age at operation (years)	49 (37–80)	53 (39–69)	n.s.
Sex ratio (M:F)	21:7	26:11	—
Side (L:R)	16:12	17:20	—
Mean follow-up (months)	85 (24–184)	72 (24–180)	n.s.
Skin breakdown (n)	9	2	—
Stump bursitis (n)	3	0	—
Mean flap rotation (°)	42 (20–70)	26 (10–50)	n.s.
Mean thickness of tissue padding at end of stump (mm)	1·2 (0·6–1·9)	2·8 (1·7–5·0)	<0·05

Values in parentheses are ranges. n.s., Not significant; *Student's t test

Discussion

There are two problems after amputation. The first is stump healing, although this is not a serious problem in patients with leprosy. The second is the durability of the stump in withstanding long-term use of a prosthesis, and this is more common in leprotic patients. Shrinkage of the stump combined with imbalanced muscle action (i.e. a greater pull by the posterior calf muscles) can cause migration of the soft tissue padding at the end of the stump. This process lessens the durability of the stump when the EF technique is used. The LP technique leaves thicker soft tissue padding at the bony end and thus reduces subsequent stump problems.

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Br. J. Surg. 1992, Vol. 79, April, 342–344

Retroperitoneal necrotizing fasciitis

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Necrotizing fasciitis is a mixed infection of the skin and subcutaneous tissues with a characteristic clinical and pathological appearance. Early radical surgical excision of all affected tissue is the treatment of choice. In a series of 19 patients with necrotizing fasciitis, bacteriological assessment in 15 confirmed the mixed nature of the infection, with Bacteroides *sp. isolated from ten patients. All 12 patients who underwent radical surgical excision survived. A subgroup of patients was identified in whom the appearance of necrotizing fasciitis in the abdomen or perineum was indicative of more extensive disease in the retroperitoneal tissues. Surgical resection of all affected tissue was not feasible in these cases and the outcome was uniformly fatal, giving an overall mortality rate for the series of 37 per cent.*

Necrotizing fasciitis has been described at a number of sites[1–3] since Wilson[4] used the term to describe a number of necrotizing infections of the subcutaneous tissues, including Fournier's gangrene. These conditions displayed the characteristic clinical and pathological features first described by Fournier[5] of apparently spontaneous necrosis of subcutaneous tissues with secondary skin changes occurring as a consequence of thrombosis in nutrient vessels.

Necrotizing fasciitis is uncommon and the bacteriology of the condition unclear[3,6–9], although some consider it to lie at the extreme end of a spectrum of synergistic infections[10].

Nineteen patients with necrotizing fasciitis have been identified in 5 years (1985–1990) at three local hospitals. Retroperitoneal involvement appears to be a lethal component.

Patients and methods

Nineteen patients from three hospitals were identified in whom a diagnosis of necrotizing fasciitis was made between 1985 and 1990. The records were reviewed with respect to clinical findings, bacteriology and outcome. The information was complete apart from the absence of bacteriological information in two patients.

Results

Clinical features

The patients comprised 13 men and six women, with a mean age of 61 years. The site of the cutaneous manifestations of the disease at presentation is given in *Table 1*. A diagnosis of necrotizing fasciitis was made on admission in eight patients, at emergency surgery for abscess formation in eight, following urinary extravasation in two, and as a result of an infected sacral pressure sore in one. Underlying conditions are detailed in *Table 2*. Other associated problems included diabetes mellitus (four patients), hemiplegia (four patients), alcohol abuse (two patients) and local radiotherapy (one patient).

Bacteriological findings in 17 patients showed the presence of multiple organisms in 15; a total of 56 organisms were isolated from the initial cultures. The commonest organisms isolated were *Bacteroides* sp. (ten patients), followed by *Escherichia coli* (eight patients) and anaerobic streptococci (seven patients). Although clostridial organisms were isolated in four patients the clinical features were those of necrotizing fasciitis rather than gas gangrene.

Treatment and outcome

Twelve patients survived after prompt radical surgical excision, antibiotics, and faecal or urinary diversion (appropriate in seven patients). In two patients active surgical intervention was deemed inappropriate because of co-morbidity, and both succumbed to overwhelming sepsis despite appropriate antibiotic therapy.

Of most interest was a group of five patients who presented with apparent perineal or flank fasciitis. Despite early diagnosis and operative intervention, this involved extensive retroperitoneal tissue necrosis and was technically irresectable. Further details of these five patients are given below.

Patient 1. A 68-year-old man with diverticular disease was admitted with necrotizing fasciitis of the perineum and scrotum. Involvement of the perirectal tissues was found and at laparotomy the process extended into the retroperitoneal tissues. Despite carrying out abdominoperineal excision of the rectum and distal sigmoid colon, it was not possible to remove all affected retroperitoneal tissues. Despite antibiotic therapy the patient died 48 h later from overwhelming sepsis.

Patient 2. A 70-year-old man developed necrotizing fasciitis of his penis, scrotum and lower abdominal wall. Laparotomy revealed an irresectable caecal carcinoma with hepatic secondaries. Extensive necrotizing fasciitis of the retroperitoneal tissues extending into the pelvis and peritoneum was found. It was not possible to remove all affected tissue and the patient died 48 h later.

Table 1 *Site of cutaneous appearance of necrotizing fasciitis in 19 patients*

Site	*n*
Perineum/genitalia	9
Buttock/thigh	6
Abdominal wall	2
Chest wall	2

Table 2 *Predisposing pathology in 19 patients with necrotizing fasciitis*

Predisposing pathology	*n*
Colonic perforation	5
Perianal/ischiorectal abscess	3
Other abscess	3
Urinary extravasation	2
Local trauma	2
None identified	2
Sacral pressure sore	1
T cell lymphoma	1

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Br. J. Surg. 1992, Vol. 79, April, 342–344

Retroperitoneal necrotizing fasciitis

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Surgical workshop

Br. J. Surg. 1992, Vol. 79, April, 344

Easy delivery of the gallbladder in laparoscopic cholecystectomy: a grooved director

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Within this unit over 300 laparoscopic cholecystectomies have been performed. One problematical area is actually removing the gallbladder through the abdominal incision. The gallbladder is usually brought out through the umbilical or the upper medial incision. After dissecting it from its bed, ensuring sound haemostasis and placing a suction drain into the subhepatic space, the surgeon grasps the gallbladder at its neck and brings it into the incision. The gallbladder may be full of biliary sludge and stones, and delivery is sometimes difficult owing to hold-up at the peritoneum (even though decompression may have been performed).

To ease the problem an instrument has been devised to aid delivery of the gallbladder through the wound. It comprises a 15 × 1·5 cm piece of metal with a central groove (*Figure 1*). The instrument is introduced alongside the gallbladder into the peritoneum. A knife is then slid down the groove to increase the space available by dividing the peritoneum. This manoeuvre aids delivery of the gallbladder without increasing the length of the skin wound. We have used this instrument in 18 operations when easy delivery has not been possible.

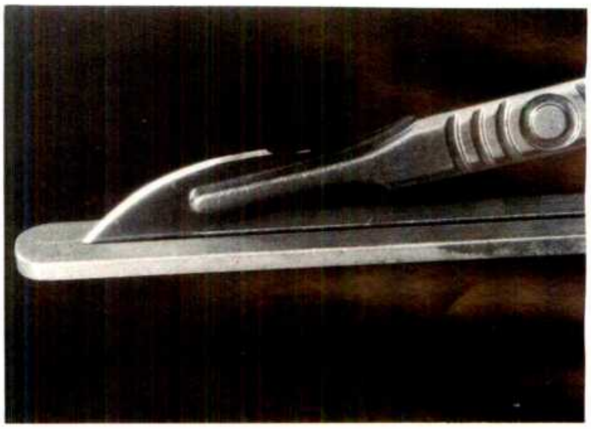

Figure 1 *Grooved director with knife* in situ

The wounds are closed in the same way with Vicryl (Ethicon, Edinburgh, UK) sutures on a J shaped needle taking a bite of peritoneum. There have been no complications after operation associated with the use of this instrument, and we have found it to be a time-saving and useful addition to the laparoscopic cholecystectomy tray.

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Glomus tumour: an analysis of 43 patients and review of the literature

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Glomus tumours are hamartomas derived from the normal glomus body. A total of 43 glomus tumours have been seen over the past 18 years, and are reviewed. Their clinical presentations and pathology are analysed and the continuing difficulty in diagnosis is examined.

The glomus tumour was first described as a distinct clinical entity by Wood[1] in 1812, and in 1924 the histopathology was accurately described by Masson[2]. The normal glomus body, from which this tumour is derived, is an arteriovenous shunt concerned with thermoregulation. Glomus bodies are distributed throughout the body but are most numerous in the digits, palms and soles of the feet[3]; histologically they consist of an afferent arteriole, an anastomotic vessel, and a collecting venule. In addition, there are smooth muscle cells and epithelial-type cells, surrounded by a fibrous capsule[4].

The glomus tumour is a hamartoma which morphologically comprises endothelial lined vascular spaces (the canal of Sucquet–Hoyer) surrounded by epithelioid cells, termed glomus cells, which are the main cell type. There is, however, a wide variation in histological appearance, with three main types being described: a vascular form, a myxoid form and a solid form, depending on the predominant cellular pattern within each tumour[2]. In addition, non-medullated nerve fibres are found in close association with these glomus cells[5]. Some pathologists have failed to demonstrate a significant number of nerve fibres in the glomus tumour and have suggested that their presence is secondary to the incorporation of normal nerve fibres[6]. Macroscopically, glomus tumours have a reddish-purple appearance, but those more deeply situated in the dermis may have no obvious external features, and this may cause diagnostic difficulties. They have been confused with neuromas, melanomas, and gouty tophi[3].

This type of tumour is uncommon (for example comprising only 1·6 per cent of a series of 500 consecutive primary soft tissue tumours of the extremities[7]) but it can occur at any age and at any anatomical site, with a predilection for the subungual region. The common clinical presentation is usually a painful, tender nodule. The pain is often excruciating and has been described as burning or bursting, can be paroxysmal in nature, and may be aggravated by changes in the environmental temperature, especially by cold[8]. In the adult, these tumours usually present as solitary lesions, with only 2·3 per cent of cases having multiple lesions. In children multiple lesions are more common, with one series reporting that 26·3 per cent of patients under the age of 16 years with glomus tumours had multiple lesions[9].

This report analyses the clinical features and examines the continuing difficulties in diagnosis of patients presenting with glomus tumours.

Patients and methods

Patients with glomus tumours treated in the Aberdeen group of hospitals between 1972 and 1990 were identified by a computer search of the Department of Pathology records. A retrospective analysis of the case notes was carried out recording, age, sex, site and size of lesions, presenting symptoms and preoperative diagnoses.

Results

Age and sex distribution

A total of 43 patients, 27 male and 16 female, who underwent surgical removal of a glomus tumour were identified. The mean(s.e.m.) ages of the male and female groups were 50(4) and 39(3) years respectively. The age distribution at presentation for both sexes is illustrated in *Figure 1*.

Anatomical site

The tumours were located at various sites of the body with the 43 cases distributed as follows: hand, 16 (subungual, ten; volar aspect of distal phalanx, four; other sites, two); upper limb, 16 (elbow, five; forearm, eight; shoulder and wrist, three); lower limb, seven (thigh and lower leg, six; volar aspect of the distal phalanx, one); neck, two; abdomen, one; and coccyx, one.

There was a difference between sexes in the anatomical site of the tumour. In male patients only five of 27 tumours were found in the digits, while in female patients, eight of the 16 tumours were located in the digits. In female patients, 12 lesions were found in the upper limb and in male patients 17 lesions were in this location.

Clinical history

The most characteristic symptom of the glomus tumour was pain. In 34 of the patients pain was the major symptom, which was commonly described as excruciating and precipitated by pressure on the lesion in all cases. Only two patients complained of worsening of pain with changes in the ambient temperature. Pain was experienced by nine of ten patients with a subungual glomus and by four of six with a glomus on the other parts of the digit. When the glomus was located centrally seven of 19 patients experienced no pain. The nine patients who did not

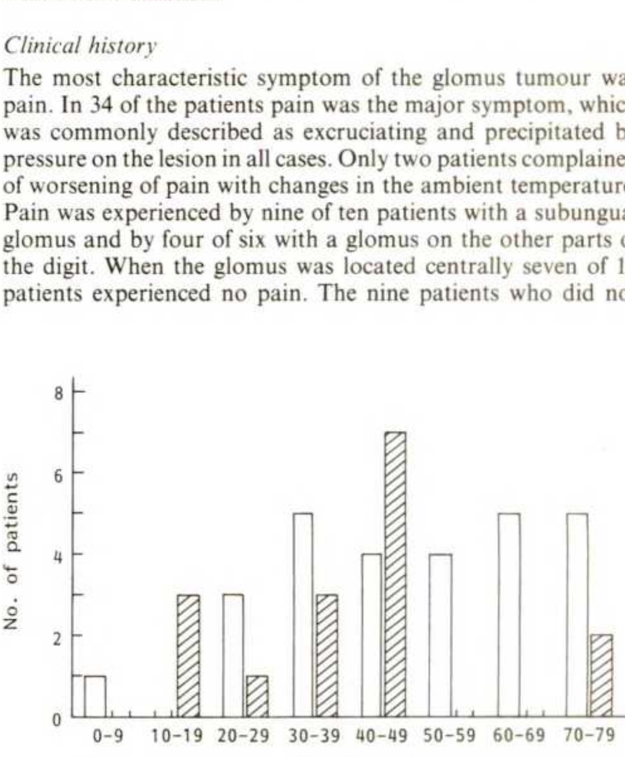

Figure 1 *Age distribution of male* (□) *and female* (▨) *patients presenting with glomus tumours*

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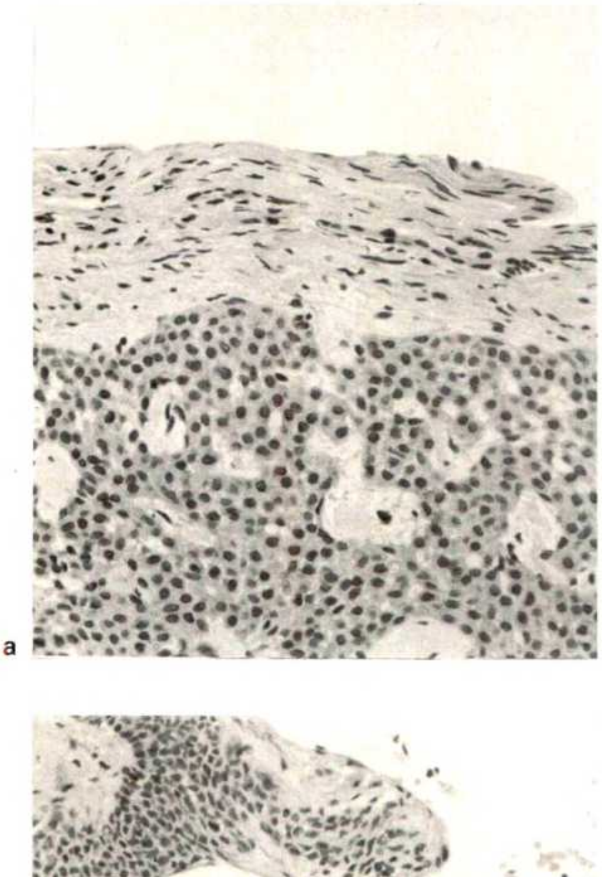

Figure 2 **a** *'Solid' type of glomus tumour, well encapsulated and consisting of solid sheets of glomus cells and inconspicuous vascular lumina. (Original magnification ×66).* **b** *'Glomangioma', unencapsulated and comprising ectatic vessels with a narrow peripheral corona of glomus cells. (Original magnification ×66)*

experience pain presented with a skin nodule. Discoloration was a characteristic feature; the glomus tumour was a reddish-purple colour in 30 patients. There was no discoloration in 13 patients. The single patient with the coccygeal glomus tumour presented with severe pain on sitting down, and on examination had a skin sinus which was extremely tender on palpation. All patients presenting with pain were relieved by surgical removal of the lesion but no long-term follow-up data are available. No patient has presented again with recurrence of the lesion or with pain.

Size and number of lesions

In 33 patients the lesion was < 1 cm in diameter, and in seven of these < 0·5 cm in diameter. Ten tumours were > 1 cm in size but only two were > 1·5 cm. There were mutiple tumours in four patients (three male and one female) and these patients had a first degree relative who had multiple glomus tumours.

Difficulty in diagnosis

A correct diagnosis was made by the referring practitioner in only eight of the 43 patients; the hospital practitioner was correct in 21 of the 43 cases. The most common erroneous diagnoses included pigmented naevi, melanoma, neuroma and 'skin nodule'. The coccygeal glomus presented as a small 'pit' over the coccyx with coccydynia, and was wrongly diagnosed as a pilonidal sinus.

Pathology

A review of the histological appearances of 40 of the glomus tumours (details of three having been lost from the archives) was performed. There were 16 glomus tumours classified as the 'solid' type (*Figure 2a*), and 17 the vascular (glomangiomatous) variety (*Figure 2b*). The remaining glomus tumours were of variable cellularity. Encapsulation was present in 18 tumours; 15 of these patients experienced pain. There was no encapsulation in 18 tumours (11 patients had pain) and in a further four encapsulation was incomplete, but all patients experienced pain.

Discussion

Glomus tumours, although relatively uncommon lesions, often pose diagnostic difficulties for the clinician and can be found at any site of the body surface. In this study, they were found to be more common in male patients than female with a ratio of 1·7:1, in contrast to the findings of Tsuneyoshi and Enjoji[5]. These authors found the tumours were almost twice as common in female patients, but described a similar anatomical distribution according to sex. In female patients, glomus tumours are most common in the digits, while in male patients they are more frequent elsewhere. Glomus tumours are usually single lesions, with multiple glomus tumours occurring in the same individual very rarely. Multiple tumours are more common in children[10], and an autosomal dominant pattern of inheritance has been described[11].

The continuing difficulty in correctly diagnosing glomus tumours was illustrated in this study, with only 19 per cent of referring practitioners and 49 per cent of hospital practitioners making the correct diagnosis. The fact that such tumours are uncommon may explain this difficulty, although the clinical triad of (1) excruciating paroxysmal pain, (2) tenderness and (3) cold sensitivity, is diagnostic[8]. In addition, the reddish-purple discoloration is a characteristic finding[7]. In this series, 79 per cent of patients presented with pain that was exacerbated by direct pressure on the lesion, and 70 per cent had a reddish-purple discoloured lesion. To improve diagnostic accuracy plain radiography may be of value for lesions in the hand, with a smooth erosion of cortical bone found in 22–60 per cent of patients[12]. Arteriography has been used but has not become an established procedure[13,14]. High resolution, high frequency sonography has been advocated, but unfortunately the ultrasonographic features are non-specific[3]. Treatment should be complete excision with removal of the capsule because of the risk of recurrence[15]. If the tumour cannot readily be localized on clinical examination then the site of the lesion can be identified by careful exploration of the suspected area with a pin as described by Love[16].

The possibility of malignant change in a glomus tumour has been examined previously. Local invasion of the capsule around the glomus tumour has been reported to occur in 1–2 per cent of cases[9], although others have found no evidence of local invasion[8,15]. Local recurrences following excision have been reported[17–19], but this may simply represent inadequate excision rather than infiltrative growth. None of the patients reported in this series had evidence of capsular or local invasion. There have been three reports of 'malignant' glomus tumours[4,20,21] and these have been examined in detail by Murray and Stout[4]. They concluded that two of the reported 'malignant' glomus tumours could not be classified histologically as glomus tumours, and in only one case could the tumour be histologically classified as a 'malignant' glomus tumour.

Coccygeal glomus tumours, which are rarely reported in the literature[22], may mimic a pilonidal sinus and may present as a rare cause of coccydynia.

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Improved technique for polytetrafluoroethylene bypass grafting: long-term results using anastomotic vein patches

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Results of peripheral arterial bypass using polytetrafluoroethylene grafts have remained poor in comparison with those using saphenous vein grafts, particularly for anastomoses to tibial and peroneal vessels. A simple modification to the conventional operative technique, involving the incorporation of a vein patch into the distal anastomosis, has enabled considerable improvement. Five-year patency rates of 71 per cent for popliteal and 54 per cent for infrapopliteal grafts have been achieved in a series of 256 patients operated on between 1982 and 1989.

Autologous vein has been the preferred graft for infrainguinal arterial reconstruction since the use of reversed saphenous vein was first described in 1949 by Kunlin[1]. However, not all patients have a vein of sufficient length and calibre, particularly if the distal anastomosis is beyond the popliteal trifurcation. Probably the best alternative material currently available is the prosthetic polytetrafluoroethylene (PTFE) graft, first introduced for clinical use in the USA in 1974 and in the UK in 1976[2].

Preliminary reports from the USA and Australia were largely optimistic[3–10] in contrast to most UK experience[11,12]. Unfortunately, these optimistic reports have proved premature; the longer term patency figures for PTFE grafts are poor, particularly for anastomoses to tibial and peroneal vessels[10,13–23]. The observation that there is a substantial number of patients with critical, limb-threatening ischaemia in whom the use of a PTFE graft represents the only alternative to amputation provides a rationale for research into methods to improve patency rates. In this paper the results of 256 patients operated on between January 1982 and December 1989 using a simple modification of the conventional surgical technique are reported. The method involves the incorporation of vein patches into both distal and proximal anastomoses. The main theme of this paper relates to the distal vein patch, but the proximal patch will be described for completeness although its benefits remain unproven. As a consequence of experience gained since its introduction[24], refinements have been made to the present technique.

Patients and methods

Operative technique

Under general anaesthesia the arteries were exposed using standard incisions. The popliteal, posterior tibial and proximal peroneal vessels were approached medially. The distal peroneal artery was exposed laterally with excision of a length of fibula[25]; grafts to this vessel and the anterior tibial artery were routed in a lateral subcutaneous situation passing deep to the sartorious muscle and then lying on the fascia lateral to the knee joint. A short incision, kept clear of the line of the graft, was occasionally required above the knee to facilitate fashioning of the tunnel. For infrapopliteal procedures dissection of the recipient artery was restricted to the presenting aspect only, with no circumferential dissection, no slinging, and without the use of arterial clamps. The conventional method for the construction of the distal anastomosis involves both circumferential mobilization of the recipient artery and the application of occluding clamps. Of necessity both these procedures are traumatic and have several serious drawbacks[26–28]. To avoid these problems, prompted by an article by Bernhard[29] in 1981, we introduced the use of a sterile pneumatic tourniquet for those infrapopliteal procedures where back-bleeding remained a problem despite inflow occlusion.

Construction of the distal anastomosis

Initially non-supported 6-mm diameter grafts were used until the introduction of externally supported prostheses. Before tailoring the PTFE it was necessary to remove the supporting spiral from an Impra graft (Impra, Ascot, UK) or rings from a GORE-TEX graft (W. L. Gore, Woking, UK) over a length of about 3 cm. A U shaped slit of 1 cm or slightly less was then made on the underside of the graft, angled minimally to ensure that the PTFE lay almost parallel to the artery (*Figure 1*).

The arteriotomy should be 3–4 cm in length, at least four to five times longer than the diameter of the 6-mm PTFE conduit. Graft-to-artery anastomosis was carried out using 6/0 polypropylene or GORE-TEX sutures. The first six continuous heel stitches were inserted in parachute fashion or, if the artery was <2 mm in diameter, four interrupted sutures were used. The graft was then slid down into position and suturing completed along each side. The PTFE was next incised in line with the arteriotomy, to a point 2 cm proximal to the heel of the anastomosis. The limit of this incision was also fashioned in a U shape and the surplus graft trimmed as shown by the dotted lines in *Figure 2*. A vein patch, which should be as large as possible, was harvested from wherever available and used to close the elliptical defect in the anastomosis. Placement of the patch was begun distally

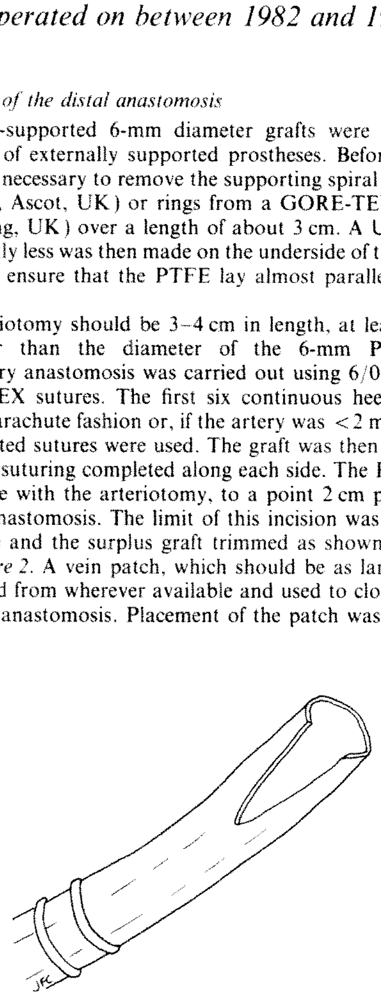

Figure 1 *The external support of the polytetrafluoroethylene is removed over a length of 3–4 cm and a short (1 cm) U shaped slit cut as shown*

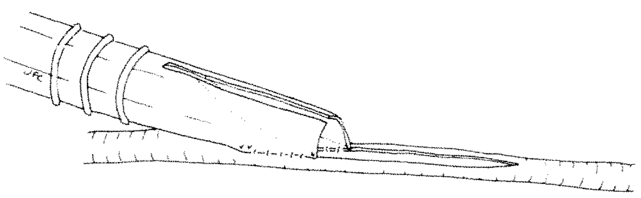

Figure 2 *The heel of the graft is sutured and slid down in parachute fashion. Suturing is completed along each side. Note the narrow angle between the graft and the artery. The polytetrafluoroethylene is incised over a length of 3 cm. The proximal limit is fashioned in a U shape, the surplus graft being trimmed as shown by the dotted lines*

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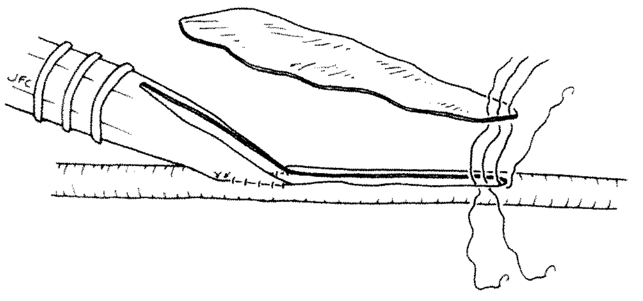

Figure 3 *The critical distal interrupted sutures between the vein patch and artery are all inserted under direct vision before any are tied*

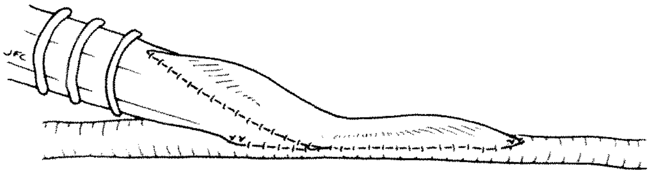

Figure 4 *Incorrect narrowing at the waist of the patch owing to excessive indrawing of the vein at the limit of the polytetrafluoroethylene–artery anastomosis*

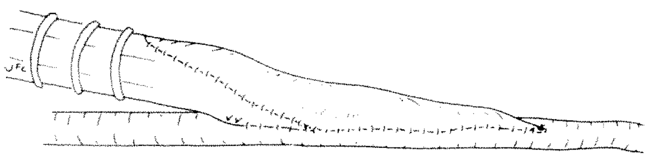

Figure 5 *Correct appearance of the completed vein patch which is tapered smoothly to enable a gradual reduction in diameter*

by using six to eight 6/0 or 7/0 interrupted sutures, all inserted before any were tied (*Figure 3*). Several more interrupted sutures were then placed on each side and a continuous suture completed the major part of the anastomosis. At the proximal limit of the graft incision, two further interrupted sutures were employed.

There was a potential for relative narrowing at the point representing the distal limit of the PTFE–artery anastomosis (*Figure 4*). This could be largely avoided if the graft was trimmed appropriately and the patch carefully placed so that the widest part overlay this area. Insertion of sutures in the vein at slightly wider intervals than on the artery or graft at this point prevented indrawing of the patch and the final appearance was more satisfactory (*Figure 5*). The vein patch varied between 5 and 6 cm in length: 2 cm along the graft, 1 cm across the PTFE–artery anastomosis, and 2–3 cm along the recipient vessel. While a gentle bulge was considered acceptable this should not be excessive, and the patch should taper distally to enable a smooth transition from the 6-mm graft to the artery which may be as small as 1·5 mm in diameter. When the available patch was wide, more of the PTFE was trimmed, thereby maximizing the amount of vein incorporated in the anastomosis. Because of limited access to the below-knee popliteal artery it was often easier to suture the vein to the PTFE before insertion of the graft in the tunnel.

Proximal anastomosis

After a conventional end-to-side anastomosis, a 3-cm longitudinal incision was made across the inlet of the graft and closed with a vein patch as shown in *Figure 6*.

Ancillary measures

Aspirin (300 mg daily) was started before surgery and continued after operation. Patients were administered 5000 units heparin intravenously before clamping and the dosage was increased to 10000 units for anastomoses beyond the popliteal trifurcation. Anticoagulation after operation was not employed. Preoperative and postoperative administration of prostaglandin E_1, in the form of alprostadil, or iloprost was used for infrapopliteal grafts. Routine arteriography after reconstruction was performed in all cases, any technical errors or problems corrected immediately, and a further film taken to confirm a satisfactory situation.

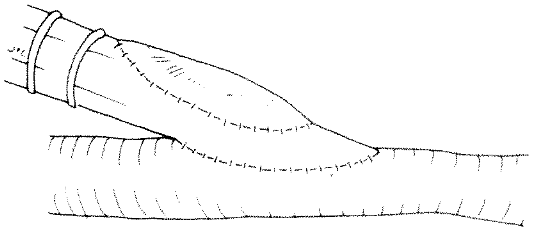

Figure 6 *In the proximal anastomosis a 3-cm vein patch is inserted across the inlet of the polytetrafluoroethylene graft*

Results

Between January 1982 and December 1989, 256 PTFE bypass procedures were performed. Follow-up extended from 1 to 9 years and detailed information, which was obtained independently of the principal surgeon, was available for 251 of the patients. Five were not traced and have been treated as failures from the last known date of patency.

All patients underwent full investigation before operation, including non-invasive Doppler ultrasonographic ankle artery pressure measurements and arteriography. Patency of the grafts was assessed by clinical examination and by Doppler ultrasonographic arterial pressure studies (and sometimes Vasoscan; Sonicaid, Chichester, UK) repeated at 3, 6, 9 and 12 months and subsequently at yearly intervals. Any patient who showed a reduction in ankle artery pressure or developed recurrent symptoms underwent further arteriographic studies. Some patients were chosen at random for follow-up arteriography. *Figure 7* shows a graft to the posterior tibial artery 4 years after operation.

Most of the patients were elderly, high-risk cases with critical limb ischaemia: 63 per cent were over 70 years old and the mean age was 72 years, 6–7 years older than in most published series. Fifty-nine per cent were men, 48 per cent smokers and 22 per cent diabetics. The procedures were carried out for limb salvage (including all infrapopliteal bypasses) in 72 per cent of cases, the remainder for severe claudication. Limb salvage implies the presence of unremitting rest pain, superficial skin necrosis or frank gangrene. For these patients the maximum ankle artery systolic pressure was below 50 mmHg and the mean preoperative ankle:brachial blood pressure index was 0·18 (excluding diabetics).

Of the operations performed 32 per cent were to an infrapopliteal vessel (*Figure 8*) and 53 per cent were to a single vessel or to an isolated popliteal segment (*Figure 9*). Previous reconstructive procedures in the same limb had been carried out in 58 (36 per cent) of the 161 limbs undergoing a below-knee procedure and nearly half of these had undergone two or more previous operations. In most patients autologous vein was not available but in a few in whom it was available the severity of scarring in the groin was considered to preclude its use and PTFE was preferred.

Primary patency

All data were evaluated using life-table analysis. The significance of differences between subgroups of cases was assessed using the procedure of retrospective classification and the log rank test[30]. The overall primary patency rate at 1 year was 85 per cent, at 3 years 74 per cent, at 5 years 65 per cent and at 8 years 51 per cent (when 17 grafts remained at risk). The figures for above- and below-knee popliteal procedures combined are 91 per cent at 1 year, 81 per cent at 3 years, 71 per cent at 5 years and 54 per cent at 8 years. The comparable figures for tibioperoneal grafts are 74 per cent at 1 year, 58 per cent at 3 years and 54 per cent at 5 years (when only

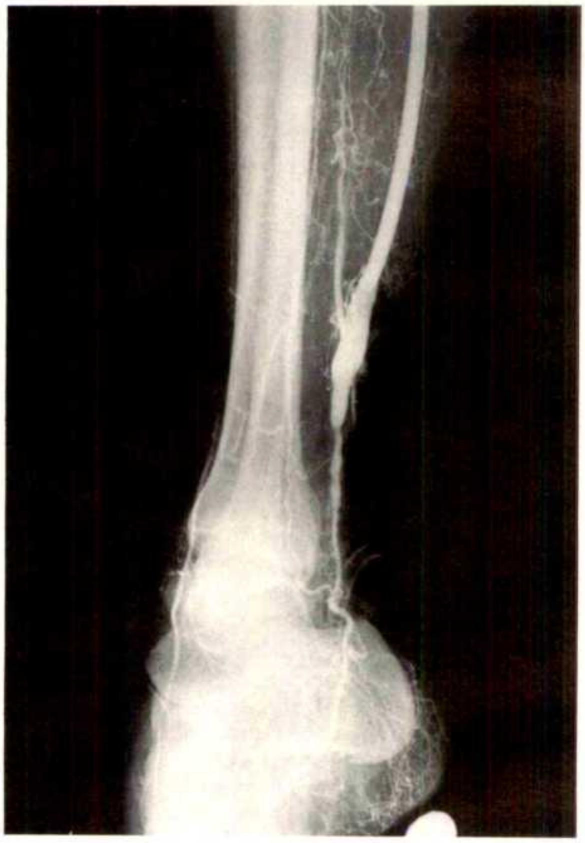

Figure 7 *Arteriogram 4 years after a polytetrafluoroethylene bypass graft to the posterior tibial artery. Note the mild outlet stenosis*

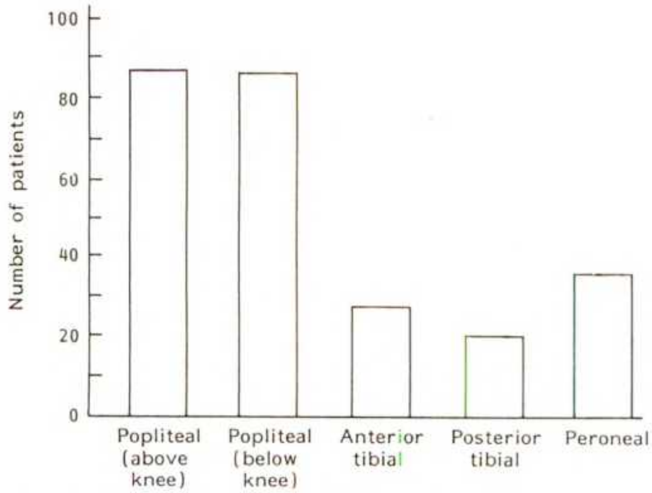

Figure 8 *Sites of distal anastomosis in 256 grafts (256 patients)*

nine grafts were at risk, reflecting the higher mortality rate in this group) (*Figure 10*).

Separate analysis for each site of distal anastomosis showed no significant difference between above- and below-knee femoropopliteal bypass ($P > 0{\cdot}25$). However, both above- and below-knee popliteal bypasses had significantly better patency rates than femorotibial/peroneal bypasses ($P < 0{\cdot}05$, *Table 1*). There was no significant difference between those patients with poor (0–1-vessel) *versus* good (2–3-vessel) run-off ($P > 0{\cdot}75$), or between diabetics and non-diabetics ($P > 0{\cdot}90$).

Secondary procedures

Secondary intervention to reopen occluded grafts was carried out in 26 instances and all but five of these grafts failed within 2 years, making the difference between primary and secondary patency rates too small to be of any practical significance. Thirteen other patients had the graft replaced or a new distal extension added and these were treated as entirely new procedures.

Graft failure

During a mean follow-up period of 35 months 71 grafts failed; six did so immediately despite initially satisfactory operative arteriograms and several attempts at clearance. All were bypasses to ankle or foot level, associated with poor run-off and mostly involving anastomoses to vessels $<1{\cdot}5$ mm in diameter. Early amputation was invariably required. Amputation was also required for 16 patients with grafts failing at a later date and five others with patent grafts. Equal numbers of

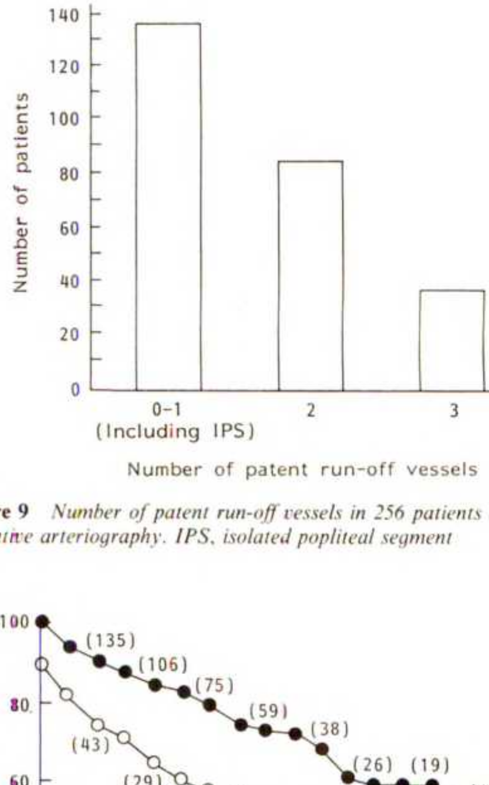

Figure 9 *Number of patent run-off vessels in 256 patients assessed by operative arteriography. IPS, isolated popliteal segment*

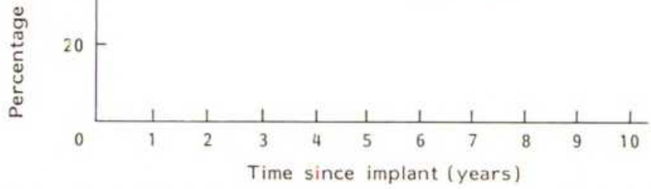

Figure 10 *Life-table curves comparing primary patency of all popliteal grafts with infrapopliteal grafts.* ●, *Above- and below-knee femoropopliteal grafts;* ○, *femorotibial/peroneal grafts*

Table 1 *Patency rates for above-knee, below-knee and tibioperoneal grafts at 1, 3 and 5 years after operation*

Category	Number at risk at start	Percentage cumulative patency		
		1 year	3 years	5 years
Above-knee	87	94	85	77
Below-knee	86	88	77	65
Tibioperoneal	83	74	58	54

Table 2 *Causes of graft failure*

Cause of failure	Number	Mean time to failure (months)
Progression of disease	19 (27)	36
Anastomotic hyperplasia	10 (14)	27
Kinking	8 (11)	21
Poor run-off	7 (10)	<1
Myocardial infarction/cardiac failure	7 (10)	10
Embolization	4 (6)	14
Technical problems	2 (3)	<1
Infection	2 (3)	1
Antithrombin III deficiency	1 (1)	20
Acute aortic thrombosis	1 (1)	5
Unknown	10 (14)	33
Total	71 (100)	–

Values in parentheses are percentages

above- and below-knee amputations were performed but the rate of amputation after failure of tibioperoneal grafts was 25 per cent higher than that after failure of popliteal grafts. Eleven patients (16 per cent) with occluded grafts died within a short time of blockage and without any further procedure. Limb salvage rates for surviving patients were 96 per cent, 88 per cent and 80 per cent, respectively, at 1, 5 and 8 years after operation. An analysis of the causes of failure is shown in *Table 2*.

Causes of death

A total of 87 patients died during the study period; most of these were among the group operated on for limb salvage. Myocardial infarction, cardiac failure and cerebrovascular episodes accounted for 65 per cent of deaths.

Discussion

PTFE grafts have been available for clinical use for more than 10 years. Although they represent a considerable improvement on previous prosthetic materials, results obtained using PTFE remain inferior to those for saphenous vein. Such figures have led to disillusion with the use of prosthetic grafts, particularly to the below-knee popliteal and more distal vessels, and many surgeons will not employ them even for limb salvage[16,31]. Unless these patency rates can be improved reconstruction will continue to be denied to those patients in whom autologous vein is not available.

In 1982, prompted by our poor early results using PTFE for infrapopliteal bypass, we carried out an investigation into the probable causes of failure of grafts inserted over the previous 4 years. Anastomotic hyperplasia was responsible for approximately 25 per cent of late failures (more than 1 month after insertion) and was second only to progression of distal disease[32]. The few other detailed studies into the causes of PTFE graft failure have described a similar incidence of anastomotic hyperplasia[17,33,34], which in our experience characteristically develops at the outlet of the graft and within the recipient artery, around and just beyond the anastomosis. The same site predilection has been shown experimentally by Oblath *et al* [35] and Sottiurai[36] and clinically by Echave *et al.*[37]. Narrowing is less often seen at the proximal anastomosis[32].

In 1982 the concept that the problem might be helped by the planned insertion of a vein patch across the anastomoses arose because of two earlier observations. First, we had successfully reopened four of five occluded bypasses by thrombectomy, removed a quite separate, well organized, smooth, adherent hyperplastic layer, and inserted a vein patch across the distal anastomosis. Second, in a small series of patients in whom PTFE had been anastomosed to the popliteal artery above the knee and a vein extension taken directly from the PTFE to a below-knee vessel, follow-up arteriography had demonstrated complete absence of narrowing at the PTFE–vein anastomosis up to 5 years later.

Although the employment of vein patches has led to a reduction in the incidence of anastomotic hyperplasia, this alone cannot fully explain the improved results and it is proposed that the main advantage may relate directly to the intrinsic properties of the vein[38]. The inevitable oval distortion of the arterial lumen which occurs at the toe of a direct PTFE–artery anastomosis has been shown experimentally to be largely eliminated by incorporation of a vein patch[38,39]. The biological consequences of such oval arterial distortion are not yet known but the associated increased turbulence might well promote the deposition of anastomotic hyperplasia.

The vein patch may also act to reduce the compliance mismatch considered by many to be important in the production of anastomotic hyperplasia[40–42]. The presence of a compliant segment will reduce anastomotic resistance, particularly in small vessels[43], and might shift the deposition of hyperplasia to the wider, less critical, PTFE–vein patch situation. A further and as yet unproven possibility is that release of fibrinolytic and antiplatelet substances from the live vein endothelium has a beneficial effect, reducing the local formation of neointima.

In 1979 Siegman[44] described the use of a venous cuff; this technique has been developed further by Miller *et al.*[45], who reported encouraging early clinical results in 1984, and by Wolfe *et al.*[46,47]. However, theoretical disadvantages of the cuff technique relate to the increased turbulence caused by the anastomotic reservoir[48] and to the impossibility of achieving a narrow angle between the PTFE and artery, both of which may increase turbulence and shear stress[48,49]. This might help to explain the reported high early failure rate of 33 per cent within 30 days of insertion[46].

Differences in case selection, operative technique and overall management make comparison of different series difficult. Nowhere is this better exemplified than in the recent report by Whittemore *et al.*[23], in which the average ankle:brachial pressure index for patients having PTFE grafts for limb salvage was 0·47, compared with a figure of 0·18 in the present series. In an attempt to eliminate intercontinental differences and achieve a worthwhile comparison with similar cases we have compared our results with those of three large series of PTFE grafts reported by UK surgeons[14,18,50] (*Tables 3* and *4*). The present series shows more promising results despite the fact that a much larger proportion of tibial and peroneal grafts is included. This could be explained in part by the routine employment of completion arteriography[51] The value of this is most striking for infrapopliteal grafts and it is estimated that 15 per cent of grafts would probably have occluded rapidly had defects seen on arteriography not been corrected immediately.

For bypass procedures to small vessels the employment of a meticulous surgical technique is mandatory for success; even a minor error can be disastrous. In this respect it is much easier

Table 3 *Cumulative primary patency rates for polytetrafluoroethylene grafts (UK experience)*

	Percentage cumulative patency			
End of interval	Kidson *et al* [14] (*n* = 44)	Williams *et al* [18] (*n* = 180)	Williams *et al* [50] (*n* = 86)	Present series (*n* = 256)
1 month	90	70	80	96
6 months	62	50	65	91
1 year	52	40	62	85
2 years	40	29	57	79
3 years	–	18	–	74
4 years	–	18	–	68
5 years	–	18	–	65
6 years	–	–	–	56
7 years	–	–	–	56
8 years	–	–	–	51

to suture vein to a tibial vessel. The use of interrupted distal sutures enables the most important stitches to be placed under direct vision and allows for subsequent expansion of the host arterial diameter in response to increased inflow pressure.

There is little further difference between the series under consideration and it seems reasonable to assume that the vein patch may be the important factor. Retrospective comparison with our own limited earlier experience before routine use of the vein patch allows some conclusions to be drawn. In a series of 45 below-knee popliteal bypasses with vein patch a 24-month patency rate of 92 per cent was obtained, compared with an 81 per cent rate for 21 non-patched grafts. Unfortunately, the small numbers mean the difference fails to achieve statistical significance. For infrapopliteal grafts our experience of direct PTFE–artery anastomosis was limited to nine cases with a 24-month patency rate of only 42 per cent.

On the basis of ongoing assessments we feel that the vein patch is probably not very important for above-knee grafts, of some importance for the below-knee popliteal situation, and very important for infrapopliteal grafts. Most reports show superior patency rates for above-knee popliteal, compared with below-knee popliteal PTFE grafts[4,13,14,21,22,52–54], although some show no short-term[55] or long-term[15,20,23,56] difference. Cumulative 5-year patency rates vary between 22 and 75 per cent and there is no consensus regarding the effects on patency of the quality of run-off, the indication for operation, or presence of diabetes[15,16,19,20,22,23,53,56,57]. The present results are the same for above- or below-knee popliteal grafts, with an overall 5-year patency rate of 66 per cent; we agree with others[34,56] that many of the factors traditionally considered important for success or failure at these levels are of little real consequence.

It is in the situation relating to tibioperoneal PTFE grafts that the vein patch appears to make a major impact. Because of the generally very poor results for these procedures few large series have been reported and the follow-up period is short, often with small numbers of patients at risk[16,20,21,23,47,52–54,58,59] (*Table 5*). The best results previously reported are those of Christenson *et al.*[53] who showed 2- and 5-year patency rates of 52 per cent and 49 per cent respectively. These authors used daily postoperative intravenous infusions of 500 ml dextran for 5 days. Likewise Flinn *et al.*[59], in a series of 75 patients, reported patency rates of 45 per cent at 2 years and 37 per cent at 4 years, using thin-walled PTFE and postoperative anticoagulation. Improved results may also be obtained by aggressive preoperative interventional radiology, enabling the use of more distal inflow sites and in some cases avoiding the need for salvage surgery altogether. It is our experience, and that of Whittemore *et al.*[23], that failure of a distal graft for limb salvage during the first year almost invariably results in amputation. Although several reports have suggested that failed distal grafts lead to higher amputation levels[60,61], this has not been our experience or that of some others[16,62].

Table 4 *Limb salvage procedures, run-off, and distal anastomosis level in the series described in* Table 3

	Percentage cumulative patency			
	Kidson *et al*[14] (*n* = 44)	Williams *et al*[18] (*n* = 180)	Williams *et al*[50] (*n* = 86)	Present series (*n* = 256)
Limb salvage procedures	80	90	14	72
0–1-Vessel run-off	39	50	74	53
Below-knee grafts	39	49	20	66
Tibioperoneal grafts	9	0	0	33

In conclusion, on the basis of the results over the past 9 years it appears that the incorporation of a vein patch into the distal, and possibly into the proximal, anastomosis of PTFE grafts leads to much improved long-term patency rates, particularly in the infrapopliteal situation. It is considered that the distal patch is of prime importance; the requirement for the proximal patch remains unproven. Alternative, more complicated techniques incorporating vein are available[47], but no long-term patency figures have been reported and the method described in this paper is simple, quick and proven to be effective.

This was not a randomized trial since cases were largely selected on the basis of non-availability of vein and it has not been our intention to compare PTFE with alternative materials. However, using PTFE with a vein patch produces results which are little different from those of vein in the popliteal situation; we agree with others[10,17,21,22,63] that in the above-knee situation a good case can be made for the initial employment of PTFE with preservation of the vein for future use. We do, however, believe that a 'good' vein graft is better than PTFE for distal bypass procedures; the superiority of vein at this level has been shown by many workers[10,16,20,64,65].

While an aggressive policy towards limb salvage is almost always justified, some discretion is needed, particularly in patients with a poor life expectancy. However, recent evidence[66] suggests that it is precisely this group of patients who may benefit most from attempts at limb salvage despite the presumed increased surgical risk and decreased long-term survival. Success of a prosthetic graft in limb salvage should be judged by rather different criteria than success in claudication[14]. Few elderly, high-risk patients will ever walk on a prosthesis and

Table 5 *Cumulative primary patency rates for tibioperoneal polytetrafluoroethylene grafts placed for limb salvage*

Reference		Number of grafts	Percentage cumulative patency				
			1 year	2 years	3 years	4 years	5 years
Cranley and Hafner[54]	(1982)	13	35 (2)	35 (1)	35 (1)	35 (1)	—
Christenson *et al.*[53]	(1985)	54	54 (27)	52 (25)	49 (24)	49 (22)	49 (15)
Hobson *et al.*[16]	(1985)	41	21 (6)	12 (3)	12 (3)	12 (2)	12 (1)
Veith *et al.*[20]	(1986)	98	46 (39)	34 (22)	30 (16)	12 (3)	—
Rafferty *et al.*[21]	(1987)	76	31 (16)	21 (10)	19 (9)	17 (6)	14 (3)
Flinn *et al*[59]	(1988)	75	58 (37)	45 (20)	37 (7)	37 (5)	—
Tyrrell *et al.*[46]	(1989)	30	40 (12)	—	—	—	—
Whittemore *et al.*[23]	(1989)	21	25 (4)	12 (1)	12 (1)	12 (1)	12 (1)
Johnson and Squires[52]	(1991)	37	37 (36)	26 (11)	21 (8)	7 (6)	0 (0)
Londrey *et al.*[58]	(1991)	33	38 (17)	26 (7)	7 (4)	7 (1)	0 (0)

Values in parentheses are numbers of patent grafts at risk at the start of each period their quality of life is generally poor following amputation[6,7]. In this regard we consider an overall 5-year patency rate of 65 per cent and limb salvage rate of 88 per cent to be acceptable and to justify the continued use of PTFE grafts in the absence of suitable vein

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Announcement

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The 2nd European Congress of Surgery under the auspices of Eurosurgery/Eurochirurgie will take place in Brussels in June 1992. This meeting will pursue the aims of Eurosurgery/Eurochirurgie to promote research and training in surgery.

There will be national sessions sponsored by the associations of surgery of all participating nations. Areas of topical interest will be covered in symposia and free paper sessions in areas of general interest and in the specialist fields of abdominal, thoracic, transplantation, trauma, paediatric, endocrine, plastic and vascular surgery. There will be several symposia related to surgical training.

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Predeposit autologous blood transfusion in patients with colorectal cancer: a feasibility study

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Over a 2-year period, a predeposit autologous blood transfusion service was provided for all patients undergoing elective surgery for left-sided colonic or rectal cancer in one hospital. Of 129 such patients, 28 were suitable for autologous donation. Eight of these received autologous blood only, 13 required no transfusion, and seven needed additional homologous blood. Thus, although predeposit autologous transfusion for patients with colorectal cancer is possible, only a very small proportion are likely to derive any benefit which it might confer.

In 1982, Burrows and Tartter reported an increased recurrence rate associated with blood transfusion in patients undergoing operation for colonic cancer[1]. Since then, numerous independent retrospective studies have suggested an adverse effect of blood transfusion in patients with colorectal cancer[2–7] and in those with other solid tumours[8–11], but the reasons underlying these findings are far from clear.

It is known that random donor blood transfusions have a beneficial effect on cadaver renal allograft survival[12], and it has been postulated that any effect of blood transfusion on malignancy may be immunological in nature. Indeed, blood transfusion has been shown to increase suppressor cell activity[13], and to reduce natural killer cell activity[14]. It is not known, however, which component of blood may be responsible for these phenomena, and although ferritin[15] and phagocytosis of red cells by monocytes[16] may affect lymphocyte function, there is also evidence that plasma may be the important factor in accelerating tumour recurrence[17].

Despite fairly convincing clinical and immunological evidence, however, it must be appreciated that all the studies showing an effect of transfusion on cancer recurrence in humans have been retrospective. It is therefore impossible to be certain that independent factors associated with the need for blood are not operating. Furthermore, there are a number of studies which have failed to demonstrate a statistically significant effect of transfusion on patients with colorectal cancer[18–20], and the issue is still open to considerable debate.

For this reason it would seem desirable to carry out a randomized prospective study to determine whether or not blood transfusion is harmful to patients undergoing surgery for colorectal cancer. Clearly, it would be impossible to randomize patients into transfusion and non-transfusion groups, as it would be unjustifiable to transfuse a patient who did not require blood or to withhold blood from one deemed to need it. An attractive alternative would be to compare the effects of random donor blood transfusion with that of autologous predeposited blood. Autologous blood is less likely to have immunosuppressive effects, and there is evidence from animal experiments that it has less effect than allogeneic blood on the growth of metastases[21].

Before such a trial can be contemplated, however, it is important to assess the feasibility of autologous transfusion in patients with colorectal cancer in order to determine whether sufficient numbers of patients could be recruited within a realistic period. For this reason, we have carried out a pilot study over a 2-year period in which all patients with colorectal cancer requiring elective surgery were considered for predeposit autologous donation.

Patients and methods

All patients who presented to this department with colorectal cancer requiring elective surgery were entered into the study. This group was derived from three sources: general practitioner referrals, interspecialty referrals, and those with tumours identified by the Nottingham Colorectal Cancer Screening Study Patients with right-sided colonic lesions were immediately excluded from further consideration as it has been found in this unit that such patients often require preoperative transfusion for anaemia and rarely suffer sufficient blood loss during surgery to warrant intraoperative or postoperative replacement. Patients over the age of 75 years and those with a history of carcinoma (other than basal cell carcinoma or cervical *in situ* disease) were also excluded on the basis that survival data on such patients would be difficult to interpret.

Before the remaining patients were asked to participate in the study, it was necessary for them to fulfil the criteria for autologous transfusion laid down by the British Blood Transfusion Task Force[22] (*Table 1*) If there was no contraindication, full written informed consent was obtained, and arrangements were made to withdraw the predeposited blood donations at intervals of approximately 1 week, finishing no later than 5 days before surgery All patients donating blood were given iron supplementation in the form of 600 mg ferrous sulphate per day in divided doses from the date of first donation until operation. The haemoglobin level was estimated before each donation, and if it fell below 11 g/dl donation was either deferred for 1 week or the schedule was terminated, depending on the date of operation.

Blood was taken in the manner approved by the Trent Regional Blood Transfusion Service A volume of 450 ml was withdrawn into standard donor bags containing citrate phosphate dextrose with adenine, ensuring a shelf-life of 35 days. The blood was identified by a label differing from those used for homologous blood, and carrying the patient's details and signature. Each unit was taken immediately to the blood bank where it was grouped and stored separately from the usual supplies. The blood transfusion laboratory also supplied unique donation numbers and bar codes for the purposes of identification.

In the immediate preoperative period, blood from the patient was cross-matched with the previously donated units as a final check of

Table 1 *Contraindications to predeposit autologous blood donation based on guidelines laid down by the Blood Transfusion Task Force of the British Committee for Standardization in Haematology*[22]

1. Cardiovascular disease
2. Cerebrovascular disease
3. Respiratory disease
4. Epilepsy
5. Active infection
6. History of prolonged or delayed faint after previous donation
7. Haemoglobin level of <12 g/dl in men or <11 g/dl in women

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identification, and on the day of surgery the autologous blood was made available in the usual way, with further cross-matched units from the random donor pool being used as necessary. In the event of transfusion being instituted, it was ensured that all the predeposited blood was given before any homologous blood Units which were not used were kept until the expiry date in case the patient required a late postoperative transfusion, and then destroyed.

Results

Throughout the 2-year period of the study, 157 patients with colorectal cancer were considered for elective operation. Twenty-eight were excluded because they required a right hemicolectomy, and indeed 11 of these patients needed preoperative transfusion for anaemia and only two received perioperative blood. The operations performed on all patients and the numbers requiring intraoperative or postoperative blood transfusion of any sort are given in *Table 2* Of the remaining 129 patients, 101 were excluded for a variety of reasons, the commonest of which was anaemia (*Table 3*) It should be noted that 17 patients were not entered for administrative reasons; this was usually a result of insufficient time between diagnosis and operation.

Table 2 *Breakdown of overall perioperative blood transfusion by operation*

	No. of operations	No. requiring blood
Abdominoperineal resection	32	22 (69)
Anterior resection	39	20 (51)
Sigmoid colectomy	30	8 (27)
Hartmann's procedure	6	6 (100)
Left hemicolectomy	6	2 (33)
Extended right hemicolectomy	5	1 (20)
Right hemicolectomy	28	2 (7)
Total colectomy	1	1 (100)
Subtotal colectomy	4	2 (50)
Laparotomy only	2	1 (50)
Local treatment only	4	0 (0)

Values in parentheses are percentages

Table 3 *Reasons for exclusion from predeposit autologous blood transfusion study*

	No of patients
Administrative problems	17
Anaemia	26
Ischaemic heart disease	12
Cerebrovascular disease	2
Hypertension	7
Respiratory disease	5
Previous carcinoma	5
Other medical problems	13
Age >75 years	9
Refused	5
Total	101

Table 4 *Breakdown by operation of autologous units donated, transfused and wasted*

Operation	Units donated	Units transfused	Units wasted
Abdominoperineal resection	19	13	6 (32)
Anterior resection	28	16	12 (43)
Sigmoid colectomy	10	2	8 (80)
Local excision	3	0	3 (100)
Total	60	31	29 (48)

Values in parentheses are percentages

Of the resulting 28 donors, eight received their own predeposited blood only, 13 needed no transfusion, six had supplementary homologous blood in addition to their own blood, and one patient received homologous blood only because an equipment failure rendered the 3 available autologous units unusable. The operations performed in this group and the numbers of autologous units available and transfused are given in *Table 4*.

Altogether, 60 units of predeposited blood were taken. Although an attempt was made to obtain at least 2 units from each patient, donation schedules had to be curtailed in four cases: in three because the haemoglobin level failed to recover from the first donation and fell below 10 g/dl, and in one because the patient had a profound vasovagal episode during the second donation. Thirty-one of the units taken were transfused, resulting in wastage of 29 units (*Table 4*)

Discussion

Predeposit autologous blood transfusion has been used successfully in a variety of different types of surgery and the techniques are well established[23], but its value in elective operations for cancer has yet to be fully explored. In this study, it was found that of 129 patients with left-sided colonic or rectal cancer, 45 (35 per cent) were suitable for autologous transfusion, although for administrative reasons only 28 (22 per cent) actually had blood withdrawn and stored. A total of 21 patients (16 per cent) had their transfusion requirements met by this approach, but it should be noted that only eight (6 per cent) had an exclusively autologous transfusion. If all 45 suitable patients had been included, then, by extrapolation from the observed percentages, 26 per cent of the whole group would have had their requirements met, and 10 per cent would have received autologous blood alone

The main reason for exclusion was failure to meet the requirements for autologous transfusion laid down by the Blood Transfusion Task Force of the British Committee for Standardization in Haematology[22]. In order to maintain acceptable margins of safety it is crucial that these guidelines should be strictly observed. It was disappointing to note the substantial proportion of patients excluded for administrative reasons. This occurred largely because operating time was available for the patients which would have been wasted had the operations been delayed to allow time for the donations. It is difficult to see how this could have been avoided, and many surgeons would regard a potentially unnecessary delay of 3–4 weeks before operation as unacceptable Moreover, patients would certainly find this extra waiting period stressful, although few refused to take part in the study and in fact many welcomed the opportunity to participate in their own treatment.

Strict criteria for blood transfusion were not employed The decision to transfuse during operation was left to the individual anaesthetist, and blood was given after operation only if the haemoglobin level fell below 10 g/dl. It was felt that this would be the practice in the majority of surgical units, and would therefore be relevant to a multicentre study.

A randomized trial to compare autologous with homologous blood transfusion in patients with colorectal cancer would require a very large number of participants. Even allowing for the optimistic figure of 35 per cent suitability, only about 30 per cent of all patients entered into the autologous arm of the study would be likely to receive autologous blood alone, and if the results of the trial were interpreted on an 'intention-to-treat' basis, any difference between the study and control groups would be lessened by patients not needing any blood or requiring extra homologous units

Assuming a 5-year survival rate of approximately 40 per cent in patients entered into a trial, it would take approximately 1000 transfused patients to detect a 10 per cent survival rate advantage with reasonable statistical significance (200 of 500 *versus* 250 of 500, $\chi^2 = 10{\cdot}1$, 1 d.f., 95 per cent confidence interval 4–16 per cent). As this pilot study indicates that only 30 per cent of suitable patients would receive autologous blood alone, then to put 500 such patients into the autologous arm of the trial would necessitate the randomization of 3333 patients, and if 35 per cent of patients with left-sided colonic or rectal cancer were eligible, then about 9500 patients would have to be available, assuming no administrative problems. This figure rises to 15000 patients if, as we actually found, only 22 per cent are in a position to donate autologous blood. Thus, if a centre sees 65 patients with left-sided colonic or rectal cancer in 1 year, as was the case in this study, then for the trial to be completed in 3 years, approximately 75 similar centres would have to be involved.

Another important consideration is wastage of donated blood. One of the attractions of an autologous donation service is that if the units are not used by the patients themselves they can be given to other recipients. This is not the case with patients with cancer, however, and this study indicates that almost 50 per cent of the stored blood was destroyed. Considerable time and effort are expended collecting autologous blood, both by the patient and hospital staff, and it is somewhat disheartening if many of the donations are not used.

This study found that predeposit autologous blood transfusion for patients with colorectal cancer is possible, but whether it is feasible is less clear. Certainly, if an autologous blood transfusion service is available there is no reason why patients with cancer should not benefit from it, provided that, as here, strict precautions are taken to prevent their blood from entering the random donor pool. However, it would be difficult to justify autologous transfusion primarily for patients with cancer on the present evidence, and the number of patients needed for a randomized trial which would have any chance of demonstrating a significant effect on survival times is so large as to render such a project very difficult to perform.

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The following abstracts are from the papers presented at the Silver Jubilee Annual Meeting of the Vascular Surgical Society of Great Britain and Ireland, held at the Royal College of Surgeons in Ireland, Dublin, Ireland on 20–22 November 1991.

Aortic aneurysm screening in an urban community

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As part of a community aneurysm screening programme, 3500 men aged 65–75 years, from 20 urban general practices, received a single invitation to attend ultrasonographic screening for abdominal aortic aneurysm. Screening was carried out by a trained physicist at general practitioners' surgeries, using a Pie Data 150S portable ultrasonography scanner with 3·5 MHz sector transducer. Maximal aortic diameter was measured in the transverse and longitudinal planes. The accuracy of ultrasonography was established by comparison with computed tomography in 24 patients (Standard deviation of differences between methods was 1·78 mm; standard error of the distribution of differences was 0·37 mm.)

A total of 2669 (76 per cent) men attended screening. Compliance varied between catchment areas (range 52 per cent for inner city areas to 86 per cent for suburbs). Aortic imaging was successful in 97·3 per cent of scans.

Aortic diameters >29 mm were present in 219 (8·2 per cent) screened patients; 79 (3 per cent) patients with aortic diameters >40 mm have been referred for surgical assessment and 48 have undergone aneurysm repair. Follow up by serial ultrasonographic examinations at intervals of 3 months is occurring in 140 patients with aortic diameters 29–40 mm to monitor aneurysm growth. Ischaemic heart disease was present in 21·9 per cent of patients with aneurysms ($P < 0{\cdot}01$, χ^2 test). Previous myocardial infarcts with electrocardiogram or enzyme changes were present in 18·3 per cent ($P < 0{\cdot}01$). Other peripheral vascular disease occurred in 13 per cent ($P < 0{\cdot}01$). However, association of aneurysm formation with hypertension (19 per cent) and diabetes (5 per cent) was not statistically significant compared with the screened population.

Community-based ultrasonographic screening should contribute to reduced mortality rates from ruptured aortic aneurysm. It is an inexpensive, effective method of aneurysm diagnosis with high compliance from the at-risk cohort of an urban population.

Biochemical and molecular markers for abdominal aortic aneurysm

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There are no biological markers for abdominal aortic aneurysm (AAA). This hospital is undertaking a long-term investigation of clinical, biochemical and genetic parameters in aneurysmal patients and their families which may have predictive value. Family history and ultrasonography data have been obtained, and blood drawn for biochemical and genetic analysis, in 54 patients with AAA, 28 controls and 62 relatives of AAA patients. Three patients with AAA gave a positive family history of AAA and we have identified three patient siblings with AAAs. No aneurysms were detected in the control group. A number of biochemical markers have been evaluated, including serum α_1-antitrypsin (units ml^{-1}), leucocyte elastase activity (μmol min^{-1} mg protein^{-1}) and serum lipids (mmol l^{-1}). Results were

	n	Positive family history	α_1-Antitrypsin	Leucocyte elastase	HDL cholesterol
Patients	54	6	138(10)	0·51(0·07)*	1·11(0·03)*
Controls	28	0	142(18)	0·77(0·12)	1·43(0·13)

Values are mean(s.d.). *$P < 0{\cdot}05$ *versus* controls

These data indicate that patients with AAA do not have any major protease/antiprotease imbalance, have significantly lower leucocyte elastase activities, and have lower high-density lipoprotein (HDL) cholesterol levels than control subjects. Attempts to identify predisposing genetic factors have been guided by recent observations of an association between AAA and genetic markers on chromosome 16. Data are presented on allele frequencies at two such loci in the affected and control populations that seem to show deviation from expected allele frequencies associated with the incidence of AAA.

Ischaemic colitis and aortic surgery: incidence, relevance and diagnosis

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Ischaemic colitis, although considered an uncommon complication of elective aortic surgery, has a reported incidence of 2–7 per cent[1]. Its course, usually benign, has the potential for a lethal outcome. This study examines the true incidence of ischaemic colitis using histological criteria, and also evaluates the potential of sigmoid tonometry in earlier diagnosis[2].

Twenty patients underwent colonoscopy immediately before and 5–7 days after infrarenal aortic surgery, biopsies being taken between 20 and 60 cm. Eight of these patients were also studied using sigmoid tonometry, ischaemia being defined as a mucosal pH <7.

Of six patients exhibiting histological changes of ischaemia, five were overtly symptomatic: two had mild diarrhoea, two mucus discharge with blood staining, and one sigmoid infarction. Two of these patients had normal appearances at colonoscopy. Of those patients studied by tonometry, three developed a mucosal pH suggestive of ischaemia, none being symptomatic, though only one exhibited histological changes.

This study to date suggests that colonic mucosal ischaemia is more common than generally perceived. The development of even mild diarrhoea correlates well with histological changes, and should not be disregarded. While the results of tonometry did not relate to histological changes, further work is currently under way to evaluate whether or not this simple technique is capable of providing early diagnosis.

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Activated neutrophils mediate multiple organ dysfunction following aortic aneurysm repair

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Lung, kidney and gut dysfunction are common after elective aortic aneurysm repair. Animal studies have demonstrated this multiple organ dysfunction to be dependent on inflammatory mediators (thromboxane) and activated neutrophils. This study was designed to determine whether thromboxane release and neutrophil activation following aneurysm repair can predict postoperative organ dysfunction. A total of 38 consecutive patients undergoing elective infrarenal aortic aneurysm repair were studied. Plasma creatinine levels were measured and chest radiography performed before and 6 and 24 h after operation. Patients were randomized to receive 0·3 g kg^{-1} of the hydroxyl radical scavenger mannitol (previously shown to prevent ischaemia-induced thromboxane production and neutrophil activation) or saline before aortic cross-clamping. Intraoperative plasma thromboxane (radioimmunoassay) and neutrophil activation (flow cytometric estimation of free radical production) were measured. The physiological shunt ($Q_s \cdot Q_t$) was measured after operation and the time to first passage of flatus noted.

	Thromboxane	Neutrophil activation	Creatinine	Q_s Q_t	Mean(s.d.) ileus (days)
Mannitol ($n = 22$)	121	133	107	120	3(1)
Saline ($n = 16$)	320*	706*	186*	244*	5(1)*

Values for physiological data are percentage of preoperative values. *$P < 0·05$ between groups (ANOVA)

Mannitol prevented thromboxane production, neutrophil activation and organ dysfunction. These results indicate that multiple organ dysfunction after aortic aneurysm repair may be mediated by activated neutrophils.

Esmolol but not nitroprusside protects against spinal cord ischaemia during proximal aortic cross-clamping

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Cross-clamping of the proximal thoracic aorta (PTA) results in spinal cord ischaemia in 6–40 per cent of patients. Sodium nitroprusside, used to control proximal hypertension during PTA cross-clamping, causes distal hypotension and decreased spinal cord perfusion pressure (SCPP). The hypothesis that esmolol, a rapidly acting β-adrenergic antagonist without vasodilatory properties, would control proximal hypertension without compromising SCPP was tested. During 30 min of PTA cross-clamping in mongrel dogs, proximal hypertension was uncontrolled ($n = 6$) or controlled with an infusion of sodium nitroprusside ($n = 6$) or esmolol ($n = 6$). Proximal and distal arterial pressure, cardiac output and SCPP were monitored before, during, and for 30 min after cross-clamping and a neurological deficit was sought at 24 h. There were no differences in preclamp data between the groups. Results at 20 min cross-clamping were:

	Proximal arterial pressure (mmHg)	Distal arterial pressure (mmHg)	SCPP (mmHg)	Cardiac output ($l\ min^{-1}$)	Neurological deficit (n)
Uncontrolled	144(4)	22(3)	16(2)*	3·5(0·5)*	0*
Sodium nitroprusside	108(6)†	11(3)	4(3)	5·1(0·3)†	6
Esmolol	106(3)†	27(5)*	18(4)*	1·0(0·1)†	1*

Values except neurological deficit are mean(s.e.m.). *$P < 0·05$ *versus* sodium nitroprusside, †$P < 0·05$ *versus* uncontrolled

These data show that esmolol controls proximal hypertension during PTA cross-clamping without compromising spinal cord function. However, its profound negative inotropic effect may preclude its use in patients with impaired left ventricular function.

Role for duplex ultrasonography in patient selection for superficial femoral artery angioplasty

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To improve case selection for possible superficial femoral artery (SFA) angioplasty for the treatment of intermittent claudication, the incidence of lesions suitable for angioplasty has been ascertained by angiography. Of 160 limbs studied by angiography 70 were shown to have SFA occlusion; 37 of the 70 occlusions were unsuitable for angioplasty because they started at the origin of the SFA and were all >10 cm in length. All limbs which were treated by angioplasty came from the 33 whose occlusions arose more distally

In the second part of the study, in a different group of patients, an attempt was made to identify the proximal occlusion group with ultrasonography. The SFA was scanned with a colour duplex scanner (Acuson 128) to determine patency at the origin of the vessel, and results were compared with the angiogram. Of 54 limbs ultrasonography correctly predicted patency in 53. There were 37 patent and 17 occluded origins on angiography. There was one false negative (ultrasonography incorrectly predicted a patent SFA origin).

Duplex ultrasonography accurately predicts patency of the upper SFA and its origin and provides a technique by which some patients may be excluded from selection for angiography when angioplasty is being considered.

Development of new stenoses of balloon angioplasty of the superficial femoral artery

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To elucidate the long-term effects of balloon angioplasty of the superficial femoral artery (SFA) on the vessel itself, 27 patients who have undergone 30 angioplasty procedures have been scanned using colour flow duplex ultrasonography before and at regular intervals to 6 months after angioplasty. Fifty lesions were available for such follow-up.

Localized dissection was identified in five patients; two just above, two just below and one at the site of the lesion, suggesting balloon trauma as a mechanism. Only one healed after 2 weeks by collapse of the true lumen; the other four dissections persisted up to at least 3 months. Five patients had plaque splitting, twice occurring above the lesion. Gradual deposition of thrombus occurs and one lesion has restenosed after 3 months.

Eleven patients had 12 persistent haemodynamically significant lesions at the angioplasty site. Six resolved by 2 weeks, suggesting that trauma and thrombus played an initial role; six lesions have persisted Two patients only have developed a late recurrence at the site. Seven patients, however, have developed 14 new stenoses at other sites, ten of which have persisted to date. Five of these patients have developed significant SFA origin stenoses, within 2 weeks of the angioplasty, probably related to local trauma and thrombus formation. Five other lesions have developed in four patients, three again just proximal to the angioplasty areas with thrombus identified

Balloon angioplasty may thus cause trauma and thrombus formation leading to new stenoses, especially at the SFA origin and just proximal to the original lesion.

Systemic platelet activation and local platelet deposition during angioplasty: a role for aspirin

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Aspirin is often given before peripheral angioplasty in addition to heparin during the procedure. However, the benefit of antiplatelet therapy for this indication remains unproven. In this randomized placebo controlled study the effect of two doses of aspirin on *in vivo* platelet activation and on platelet deposition at the site of angioplasty was assessed

Patients undergoing infrainguinal angioplasty were randomized to receive aspirin (300 or 75 mg) or placebo, starting the night before angioplasty. Plasma beta-thromboglobulin (BTG) levels were measured immediately before and immediately after angioplasty as a marker of *in vivo* platelet activation during angioplasty. Platelet deposition at the site of angioplasty was assessed by platelet labelling with a radiolabelled monoclonal antiplatelet antibody (P256 Fab′). Deposition was expressed as the ratio of the count at the angioplasty site to the count at the contralateral artery. Results were:

	BTG ($ng\ ml^{-1}$)*		
	Before angioplasty	After angioplasty	Platelet deposition†
Aspirin 300 mg ($n = 10$)	12 (<10–60)	33 (16–42·5)	1·27(0·072)
Aspirin 75 mg ($n = 9$)	16 (<10–25)	32 (21·5–47·5)	1·30(0·077)
Placebo ($n = 10$)	23·5 (<10–35·5)	39·5 (24–51·5)	1·49(0·090)

Values are *median (interquartile range); †mean(s.e.m.)

In all groups there was a significant increase in BTG level after angioplasty and platelet deposition at the site of angioplasty. Platelet deposition was greater in patients receiving placebo than in those receiving aspirin. These data support the use of aspirin during angioplasty.

Prospective randomized trial of the safety of intra-arterial irrigation for angioscopy

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Patients ($n = 110$) undergoing primary infrainguinal vein grafting were randomized to receive completion angioscopy ($n = 60$) or angiography ($n = 50$). All patients were monitored with pulmonary artery catheters and arterial lines.

Patient demographics, clinical status and baseline haemodynamic parameters were similar in both groups. The angioscopy group received a mean (range) bolus of 321 (90–650) ml with a total intraoperative fluid volume of 2140 (850–5000) ml. The angiography group received a mean of 27 (8–60) ml contrast with a total operative fluid load of 2096 (650–4000) ml. Transient increases in pulmonary artery systolic pressure, pulmonary artery diastolic pressure and central venous pressure were measured during angioscopy. Although these changes were statistically significant, they were of minimal clinical relevance (1·9, 1·6 and 1·4 mmHg respectively) and returned to baseline levels within 30 min. The incidence of intraoperative interventions (e.g. diuretics or vasodilators) and the perioperative cardiac morbidity and mortality rates were no different in the two groups. Intragraft pressures recorded continuously in 24 selected cases showed that the pressures generated were within the physiological arterial range for most of the study. Provided that the principles of irrigation for angioscopy are understood and careful angioscopic technique applied, irrigation with saline solution is simple, safe and effective.

Automatic digital sphygmomanometers: a simple method for measuring ankle systolic pressure

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Increasing numbers of doctors are acquiring Doppler ultrasonographic probes to diagnose lower limb arterial disease. This is not always easy for the occasional user, and a simple method independent of observer error would be an advantage. Two inexpensive automatic digital sphygmomanometers (Omron and Ohto) were evaluated, comparing the results with Doppler pressure measurements.

Thirty-eight subjects were studied, of whom 29 were men, median age 67 (range 18–90) years. Doppler pressure indices were used to separate limbs into three groups: normal, index $>0·90$ ($n = 35$); mild arterial disease, index 0·50–0·89 ($n = 35$); and severe disease, index $<0·50$ ($n = 6$).

Both automatic machines gave clearly abnormal readings in all limbs with severe disease. For pressure indices $<0·50$, sensitivity and specificity were 100 and 77 per cent, respectively, for Omron, and 83 and 81 per cent, respectively, for Ohto. The Ohto machine was best for separating limbs with arterial disease from those without (sensitivity 88 per cent).

Three consecutive measurements were performed on 15 limbs, and showed coefficients of variability for pressure index of 0·07 (Omron) and 0·15 (Ohto). These compare favourably with the variability of Doppler ultrasonography.

These simple machines, designed to measure brachial pressures, do not require the experience needed for Doppler ultrasonographic pressure measurements, and are much cheaper than Doppler probes. They should be considered by non-specialists for evaluating patients with suspected lower limb ischaemia.

Poor long-term results after continuous-wave neodymium yttrium–aluminium–garnet laser recanalization of long femoropopliteal occlusions

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Although not theoretically ideal, use of a conventional continuous-wave neodymium yttrium–aluminium–garnet medical laser for arterial recanalization would have several practical advantages. This multidisciplinary laser system delivered by transparent sapphire-tipped optical fibres has been used for percutaneous recanalization of 32 chronic femoropopliteal occlusions in 27 patients (19 men, eight women of median age 68 (range 46–83) years).

Severe intermittent claudication was present in 24 patients and three had critical ischaemia. The median occlusion length was 8 (range 3–35) cm and lesions were not negotiable by guidewire. Laser energy was delivered at powers of 10–15 W using intermittent 1-s emissions (mean total energy 315 (range 30–1015) J). The sapphire tips used were 1·8–3·0 mm in diameter. After laser recanalization adjunctive balloon dilatation was necessary to widen the resulting lumen. All patients received antiplatelet therapy.

Initial clinical success was achieved in 22 limbs (69 per cent) with symptomatic relief and increase in mean(s.d.) ankle·brachial pressure ratio from 0·52(0·25) to 0·80(0·21) ($P < 0·001$, Student's t test). Recanalization was unsuccessful in all calcified lesions (four cases). There was a high incidence of vessel perforation (28 per cent) and wall dissection (25 per cent). Emergency surgery was not required after failed procedures. The median follow-up was 12 (range 6–20) months. By 6 months, 15 of 22 successfully recanalized lesions (68 per cent) had reoccluded. The cumulative primary patency rate at 1 year was only 12 per cent.

These disappointing results do not support routine use of this system. Clearly, modifications of the laser or delivery system, the technique, or both, are required. The aim should be to achieve sole laser recanalization without concomitant balloon dilatation.

Doppler ultrasonographic assessment of the severely ischaemic limb: a comparison of three different methods

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Preoperative assessment of the ischaemic limb should provide a thorough evaluation of calf vessel patency and pedal arch status. Pulse-generated run-off (PGR) is a new method reported to provide a more accurate representation of the distal circulation than standard Doppler ultrasonographic (SD) assessment, particularly in the presence of critical ischaemia.

The aim of this study was to see how PGR compared with Doppler assessment of the dependent limb (DD). The three methods (SD, PGR and DD) were used to assess a series of 42 severely ischaemic limbs (critical ischaemia, 31, rest pain, 11).

For calf vessel patency both PGR and DD detected more vessels than SD (103, 103 *versus* 90). In individual cases PGR and DD assessment agreed in 31 (74 per cent). Of the remainder PGR detected more vessels in five cases and DD in six.

Pedal arch status was classified as absent, incomplete or complete, and was determined by both PGR and DD. There was agreement in 26 (62 per cent) cases. Of the 16 cases which differed DD identified a more favourable run-off situation in 12.

In conclusion, PGR and DD are useful adjuncts to SD for non-invasive assessment of the severely ischaemic limb. They were equally effective in assessing calf vessel patency but DD was superior in assessing pedal arch status. DD is a simple technique which deserves wider application in this role.

Pulse-generated run-off: validation using digital subtraction arteriography

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In patients with femorodistal vascular disease no satisfactory 'gold standard' exists for the assessment of the distal circulation. It has been suggested that pulse-generated run-off (PGR), a simple non-invasive technique, is as good as (or even better than) angiography for examining the run-off circulation.

To test this hypothesis 36 patients who were to undergo superficial femoral percutaneous transluminal angioplasty (PTA) were studied. Each patient was assessed before intervention with conventional digital subtraction angiography (DSA) and with PGR. After angioplasty DSA was repeated.

Before PTA a poor correlation between PGR and DSA results was observed ($r = 0·13$). After PTA PGR was found to have accurately predicted the DSA results in most cases for distal vessel run-off ($r = 0·92$) and also accurately determined pedal arch patency when compared with DSA after angioplasty. PGR provides information about the direction of flow within run-off vessels additional to that provided by DSA, a typical waveform being observed in vessels with reversed flow.

In conclusion, PGR represents an accurate, non-invasive method for assessing distal circulation, and it may be superior to DSA for examining run-off vessels.

Calf vessel preservation in peripheral vascular disease: angiography *versus* pulse-generated run-off

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Previous angiographic and anatomical studies have suggested that the peroneal artery is the best preserved of the calf vessels in peripheral vascular disease and should be a site of preference for femorodistal bypass grafts. Calf vessel run-off assessed by pulse-generated run-off (PGR) provides a more accurate prediction of graft success or failure than angiography and may therefore give a better functional picture of vessel patency than angiography.

This study compares the presence and degree of preservation of the three calf vessels in patients with severe peripheral vascular disease using both intra-arterial digital subtraction angiography (DSA) and PGR. Thirty-four limbs in patients with ischaemic rest pain, ulceration or gangrene were studied and the results scored according to the extent and severity of disease in the peroneal, posterior tibial and anterior tibial arteries

	Peroneal	Posterior tibial	Anterior tibial
Vessel present ($n = 34$)			
DSA	27 (79)	16 (47)*	13 (38)*
PGR	31 (91)	30 (88)	27 (79)
Best preserved vessel ($n = 34$)			
DSA	22 (65)	13 (38)†	8 (24)*
PGR	16 (47)	17 (50)	17 (50)

Values in parentheses are percentages. $^*P < 0{\cdot}01$; $^\dagger P < 0{\cdot}05$ *versus* peroneal (χ^2 test)

This study shows that the peroneal artery appears the better preserved calf vessel on angiography but that this appearance may be misleading, because the more functional PGR studies show no significant difference in the patency or degree of preservation between the three calf vessels

Practical graft surveillance: an accurate alternative to duplex scanning

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Despite the development of colour duplex Doppler ultrasonography we feel there is still a need for a simple, fast and accurate screening method for graft surveillance. We have developed a scanning device, Quickscan (QS), which monitors the (x, y) position of a freely held 4 MHz continuous-wave Doppler probe The operator moves the probe in approximately 1-cm steps in order to survey the complete length of the graft and its immediate inflow and outflow tracts. Peak systolic Doppler frequency shift and (x, y) position are used to reconstruct automatically a final image, which shows the graft and any stenoses greater than 50 per cent superimposed on a grey-scale image of the patient.

The data presented consist of two sets of QS and digital subtraction angiography correlations for proximal, mid and distal graft anastomoses The first set used a simplified non-imaging format for the distal anastomosis, in a random set of graft recipients. The second, updated method imaged proximal and distal anastomoses The sensitivity and specificity of QS to stenoses of 50 per cent or more in diameter were tested by assessing both methods independently. Results were:

	Sensitivity	Specificity
Group 1 ($n = 39$)	67	100
Group 2 ($n = 54$)	82	88
Combined ($n = 93$)	76	93

Values are percentages

In our hands QS has been easier to use and is as accurate as colour duplex Doppler ultrasonography, simplifying both the assessment and reporting of graft status in a standardized surveillance protocol.

Intravascular ultrasonography with three-dimensional reconstruction

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Intravascular ultrasonography (IVUS) is a novel imaging technique that differs from conventional arteriography and angioscopy in that it can demonstrate the distribution and depth of atherosclerosis in real time. An IVUS system, using a 20 MHz transducer mounted on a 6 Fr catheter (Boston Scientific) was investigated.

In vitro work using cadaveric vessels has shown histological correlation with IVUS images in resolving the three normal arterial layers – intima, media and adventitia – in addition to plaque characterization. The differences between muscular and elastic arteries became apparent. The effects of balloon angioplasty on calcified plaque were assessed, by imaging a stenotic artery before and after balloon inflation. Serial measurements of luminal diameter were made using the probe, together with simultaneous angiograms, to compare the two techniques Good correlation with vessel diameter in two planes was obtained. However, there was no correlation with the luminal area of eccentric lesions (those whose difference in diameters, as measured at 0 and 90°, exceeded 1 mm). In most cases, the arteriogram tended to 'see' a better lumen than was present. A workstation for multiplanar formatting and three-dimensional reconstruction of the two-dimensional catheter images has been developed. This has been used *in vivo* to assess luminal size, shape and the distribution of plaque

Preliminary results indicate that IVUS shows considerable promise for quantifying luminal stenoses, plaque characterization and vessel morphology. This information should prove particularly useful in determining therapeutic options for recanalization and the guidance of endovascular devices.

Use of lightguide reflectance spectrophotometry in the assessment of peripheral arterial disease

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Doppler ultrasonographically derived systolic pressure measurements augmented by a standard exercise test are unreliable in the presence of arterial calcification ('stiff vessels'). Lightguide reflectance spectrophotometry (LRS) can be used to measure relative haemoglobin concentration (HbI) and absolute arterial haemoglobin oxygen saturation (S_{aO_2}) in the catchment area of the lightguide. To assess the value of LRS as a non-invasive test, the results obtained with LRS were compared with those from standard Doppler ultrasonographic examination in a group of non-diabetic patients.

After a standard exercise test of 1 min on a treadmill (10 per cent slope at 3·5 km h^{-1}), the HbI and S_{aO_2} on the dorsum of the foot were measured using a lightguide spectrophotometer in the following groups: normal volunteers ($n = 8$); patients with aortoiliac occlusion ($n = 5$); and patients with femoropopliteal occlusion ($n = 8$).

Normal volunteers showed a slight but not significant drop in S_{aO_2} after exercise, those with aortoiliac occlusion showed a significant fall ($P < 0{\cdot}01$) and those with femoropopliteal occlusion showed a highly significant fall ($P < 0{\cdot}001$). There was also a statistically significant reduction in HbI in patients in the second group ($P < 0{\cdot}01$), although there was no significant fall in the other two groups. There was a strong correlation between the half-recovery time for S_{aO_2} and ankle pressures in all subjects ($r = 0{\cdot}91$, $P < 0{\cdot}001$).

Preliminary data suggest that this new technique may provide an excellent and non-invasive method of assessing patients with non-compliant arteries and that it warrants further extensive study.

Indications for surgery for arteriovenous malformations

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Arteriovenous malformations (AVMs) can be disfiguring, distressing and dangerous Although embolization often succeeds, surgery may be required to control symptoms, to exclude malignancy, to excise lesions and to provide access to previously ligated vessels. In the joint vascular surgical/radiological clinic 289 patients (138 female, 151 male) were seen. Their ages ranged from 8 months to 84 years (mean 27·8 years). Areas predominantly affected by AVMs were the face and neck (31 per cent), lung (8 per cent), arm and shoulder (15 per cent), hand (6 per cent), lower limb (34 per cent) and chest wall, abdomen or pelvis (8 per cent). History of trauma to the affected region was present in 28 patients. Previous treatments included partial excision, biopsy, arterial ligation, embolization and radiotherapy. AVMs were assessed clinically and with a hand-held Doppler ultrasonographic probe. When treatment was indicated, those with a major arterial component underwent angiography. Appropriate embolization was undertaken for large or painful lesions or if bleeding had occurred. Surgery was required in 47 patients (16 per cent). Reanastomosis of previously ligated feeding vessels in seven patients restored access for embolization. Four traumatic fistulae were disconnected. Amputation of digit or limb was necessary in three cases, suspected malignancy was confirmed by biopsy in three cases. Control of AVMs by excision, plastic or orthopaedic procedures was achieved in 31 patients. During follow-up (mean 2·5 (range 0·08–10) years) two patients died (one from unrelated causes) and three underwent further surgery, including one above-knee amputation. Surgery is important in the treatment of AVMs, restoring access for embolization, relieving pain and bleeding by excision and removing uncertainty by appropriate biopsy.

Current status of polytetrafluoroethylene for above-knee reconstruction

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Although autogenous saphenous vein is the conduit of choice for infrainguinal bypasses, it has been suggested that polytetrafluoroethylene (PTFE) may be a comparable alternative for above-knee reconstructions.

Between 1981 and 1991 79 consecutive above-knee femoropopliteal PTFE bypasses were performed for critical ischaemia. The mean preoperative ankle:brachial pressure index was 0·32. Patients were prospectively evaluated to determine graft patency and limb salvage, and followed up at 3-month intervals by clinical, non-invasive and (if required) angiographic means. Results were calculated by life-table analysis.

No operative deaths occurred. The overall operative morbidity rate was 18·3 per cent: pulmonary, 8·5 per cent; wound, 5·6 per cent, and cardiac, 4·2 per cent. The limb salvage rate was 95, 89 and 84 per cent and graft patency 76, 52 and 40 per cent at 1, 3 and 5 years, respectively. Of 36 occlusions critical ischaemia re-emerged in 17 (47 per cent); secondary reconstruction was performed in 12 (71 per cent) and the remaining five (29 per cent) underwent amputation. Two secondary bypasses occluded with limb loss.

Results in terms of limb salvage using primary above-knee PTFE are comparable to those using autogenous saphenous vein. Secondary reconstruction is possible in most occlusions. We favour PTFE above the knee in the elderly and debilitated where lifespan is short and operative morbidity is minimized. In others, a policy of use of primary above-knee PTFE where feasible, preserving autogenous saphenous vein for subsequent more distal use, may optimize limb salvage.

Salvage surgery for lower limb ischaemia in the octagenarian

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Vascular surgeons are being asked to deal with an increasingly elderly population. Advanced age may be considered a relative contraindication to limb salvage surgery and quick amputation rather than a femorodistal bypass may be the preferred option in the frail older patient. A review of 50 patients over the age of 80 years presenting to this unit with ischaemic rest pain, ulceration or gangrene of the lower extremity due to peripheral vascular disease is presented.

Six patients were treated conservatively, four of whom died during the same admission. Angioplasty was attempted in 11 patients but was the sole successful procedure in only two. Twelve patients underwent primary amputation with a perioperative mortality rate of 25 per cent. Five patients had an iliac bypass procedure and the remaining 25 patients were considered suitable for infrainguinal bypass. Of the last group 14 underwent femoropopliteal bypass and 11 had femorodistal bypasses with an overall perioperative mortality rate of 12 per cent.

The mortality rate at 6 months was high, at 33 per cent in both the grafted (ten of 30) and amputation (four of 12) groups. The patients in the infrainguinal bypass group have been followed up for a mean of 9·7 months with patent grafts in 14, subsequent amputation in three and death in eight. Patients undergoing reconstruction fared better than those with amputation in terms of length of hospital stay, independent mobility and use of long-term care.

In this cohort of patients in their 80s with severe peripheral vascular disease, reconstructive procedures were possible in 32 of 50 patients. Reconstruction appears a worthwhile undertaking in the octagenarian with the prospect of a return to independent mobility.

Externally supported Dacron as a graft material for infrainguinal arterial reconstruction

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In vitro and *in vivo* studies have confirmed the high thrombogenicity of Dacron (Du Pont). The recent Medical Research Council femoropopliteal trial has suggested that antithrombotic therapy may improve the outcome of prosthetic grafts (polytetrafluoroethylene or human umbilical vein). In the light of these findings experience with an externally supported Dacron graft, a cheaper prosthetic alternative, is reviewed.

Infrainguinal arterial bypass using Dacron was performed in 105 patients. There were five postoperative deaths (4·8 per cent) and the results of the remaining 100 patients were analysed. The overall patency rates at 1 and 2 years were 62 and 55 per cent, respectively. A statistically significant improvement in 2-year patency was obtained when grafts were performed for claudication rather than limb salvage (70 *versus* 40 per cent, $P < 0{\cdot}005$). Patency of above-knee anastomoses was superior to that of below-knee anastomoses (75 *versus* 45 per cent, $P < 0{\cdot}005$). Antithrombotic prophylaxis using aspirin and Persantin (Boehringer Ingelheim) improved graft patency to approximately 90 per cent at 2 years. This difference was statistically significant when compared with a group of untreated grafts ($P < 0{\cdot}001$). Albumin preclotting did not improve graft patency.

This study has shown that acceptable patency rates can be achieved with Dacron used to treat claudication and anastomosed above the knee to the popliteal artery. Since Dacron is cheaper than the currently favoured alternatives it deserves more consideration.

Combined Miller cuff and arteriovenous fistula at the distal anastomosis of prosthetic femorodistal grafts

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Prosthetic bypass grafts to distal tibial arteries are associated with a high incidence of early graft failure and low long-term patency rates. In an attempt to improve results we have employed adjuvant arteriovenous shunts (AVSs) alone and in combination with vein cuffs (VCs)[1] at the distal anastomosis.

In a series of 264 bypasses autologous vein grafts were used in 156, prosthetic grafts with AVSs alone in 80, and prosthetic grafts with AVSs and VCs in 28. All groups were well matched for sex, age and presenting symptoms. Cumulative patency rates at 1 month were 93·8 per cent for the vein grafts, 79·4 per cent for prosthetic grafts with AVSs and 76·9 per cent for prosthetic grafts with AVSs and VCs (P not significant). At 12 months cumulative patency rates were 72·3 per cent for vein grafts, 36·6 per cent for prosthetic grafts with AVSs and 59·7 per cent for prosthetic grafts with AVSs and VCs. Prosthetic grafts with AVSs alone fared significantly worse than both autologous vein and prosthetic grafts with AVSs and VCs ($P < 0{\cdot}02$). The 12-month patency rate for the prosthetic graft with combined AVSs and VCs was similar to that of autologous vein grafts in this small series.

With an adjuvant distal AVS, the early patency of prosthetic grafts to distal tibial arteries is similar to that with autologous vein, but the longer term results with AVSs alone remain very poor. With a combination of AVS and VC, the later patency of prosthetic grafts at 12 months is significantly improved and may approach that of autologous vein grafts.

1. Miller JH, Foreman RK, Ferguson L, Faris I. Interposition vein cuff for anastomosis of prosthesis to small artery. *Aust N Z J Surg* 1984; **54**: 283–5

Vein compliance: a preoperative indicator of vein grafts at risk of developing stenosis

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The quality of run-off, inflow and the bypass conduit are the main factors in determining the outcome of femorodistal bypass. To date little quantitative physical assessment of the prebypass vein is available. Using duplex ultrasonography and venous occlusion of the long saphenous vein, the preoperative compliance of the vein was calculated. This was performed in 47 patients undergoing femorodistal bypass, compliance measurements being performed at the mid-thigh, knee and mid-calf. All patients were followed up with intra-arterial digital subtraction angiography. The mean (95 per cent confidence interval) vein compliance at the different sites was: mid-thigh 0·25 (0·21–0·29), knee 0·27 (0·20–0·34); mid-calf 0·26 (0·22–0·30). None of these was significantly different (ANOVA).

Six patients developed an angiographically proven graft stenosis. The mean follow-up was 6 months. The lowest compliance value in this group was compared with that of those with no stenosis: no stenosis, compliance 0·20 (0·16–0·24), stenosis, compliance 0·99 (0·06–0·12) ($P = 0·001$, Mann–Whitney U test).

These results show that preoperative measurement of vein compliance may identify the long saphenous vein which is at risk of developing stenosis.

Mobility following peroneal reconstruction

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Distal arterial bypass is frequently utilized for critical lower limb ischaemia. Although widespread use of the tibial artery is common, scepticism still exists regarding peroneal revascularization, and in particular the improvement in patient mobility following this procedure.

Over a 9-year period 84 distal revascularizations to the peroneal artery were performed. There were 51 men and 33 women, with a mean age of 72 years. The conduit was autogenous saphenous vein in 67 instances and polytetrafluoroethylene (PTFE) in the remaining 17. Distal insertion was to the proximal ($n = 38$), mid ($n = 27$) or distal ($n = 19$) peroneal artery. Patients were prospectively followed and assessed for graft patency, limb salvage, and mobility. Mobility was divided into three categories: independent, limited mobility, and wheelchair/housebound.

Mean(s.d.) cumulative patency rates were 85(4), 63(6) and 55(9) per cent at 1 month, 1 and 3 years after operation, respectively. The corresponding mean(s.d.) cumulative limb salvage rates for the same periods were 88(5), 65(6) and 60(8) per cent. Before operation only 16 per cent of patients were considered independently mobile, 61 per cent had limited mobility and 22 per cent were housebound. After operation these figures had improved to 45, 42 and 12 per cent, respectively.

These results suggest that reconstruction of the peroneal artery provides excellent graft patency and limb salvage rates. In addition, mobility is significantly improved. We conclude that the peroneal artery provides results which are comparable to those from the more standard tibial bypass.

Antiproliferative effects of low molecular weight heparin: a model of intimal hyperplasia in vein grafts

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Intimal hyperplasia due to smooth muscle cell proliferation is a well recognized cause of vascular graft failure. Several studies have demonstrated that the mitogenic activity of platelet-derived growth factor can be modified by heparin. In this study the efficacy of a low molecular weight heparin (LMWH) in controlling intimal hyperplasia *in vivo* has been assessed. Fifteen New Zealand White rabbits underwent interposition vein grafting of the carotid artery. Animals were randomly assigned to a control or treated group. Treated animals received 60 units anti-Xa per kg subcutaneous LMWH daily for 1 month. Animals were then killed, graft patency was assessed and the vessels then harvested for analysis of intimal hyperplasia. Intimal hyperplasia in carotid arteries and vein grafts was measured using a computerized image analysis system. A statistically significant reduction in the degree of intimal hyperplasia seen in the distal anastomoses of carotid vein grafts was achieved using subcutaneous LMWH (mean (interquartile range). control 0·44 (0·37–0·55); LMWH 0·27 (0·0–0·37); $P < 0·05$ (Mann–Whitney U test)). Grafts in the LMWH group showed an improved patency rate (70 per cent) compared with those in controls (57 per cent). This study has shown that subcutaneous LMWH effectively inhibits the development of intimal hyperplasia following vascular grafting. This effect, together with the antithrombotic effect of LMWH, may help to prolong vascular graft patency.

Arterialization, not vein harvest, is responsible for changes in vein graft contractility

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Although autogenous vein grafts (VGs) are believed to be inert conduits, there is increasing angiographic evidence to suggest that VGs can develop vascular spasm. Recent efforts to define the aetiology of vascular spasm have focused on the role of the endothelium as a modulator of vasomotor tone and on changes in contractility to various vasoactive substances. We have previously demonstrated (using an experimental model in the rabbit) that VGs *develop* serotonin sensitivity[1] and that the VG neoendothelium does not exhibit endothelium-dependent relaxation to certain agonists[2].

To characterize further the nature of these changes in contractility, an experimental sham vein graft (SVG) model to study the effect of VG harvest on VG contractility was developed.

Twelve male New Zealand White rabbits underwent sham vein grafting of the left external jugular vein (EJV). After exposure, a 2-cm segment of left EJV was excised, stored in heparinized saline and reimplanted into the left EJV. The right EJV was prepared in a similar fashion and then grafted into the right common carotid artery (VG). At 4 weeks the SVG and VG from each animal were harvested and mounted under isometric tension in an organ bath. Acetylcholine (0·1 μM) was added to the SVG and VG precontracted with noradrenaline (1 μM) to produce relaxation via the production of endothelium-derived relaxing factor (EDRF). SVG demonstrated a significant mean(s.e.m.) relaxation to acetylcholine of 68(18) per cent. In marked contrast, acetylcholine did not relax the precontracted VG. In addition, although the SVG did not contract in response to serotonin, the VG exhibited dose-dependent contraction to serotonin. These data indicate that loss of endothelium-dependent relaxation in VGs and the development of serotonin sensitivity is due not to vein harvest but is related to arterialization of the grafted vein. These changes in contractility may be contributory in the phenomenon of VG spasm.

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2. Cross K, El-Sanadiki M, Murray J, Mikat E, McCann R, Hagen P-O. Functional abnormalities of experimental autogenous vein graft neoendothelium. *Ann Surg* 1988, **208**: 631–8.

Femorocrural reconstruction with and without autologous vein: success of reintervention after graft failure

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The value of arterial reconstruction to crural vessels in conditions of critical leg ischaemia is doubted by some, particularly when prosthetic grafts are used. Primary amputation is the only alternative in these patients. The impact of femorocrural reconstruction in the treatment of this difficult problem was therefore assessed.

Between 1985 and 1990, 395 arterial reconstructions for critical leg ischaemia were performed, of which 129 (33 per cent) were to crural vessels in the lowest third of the calf (89 autologous vein grafts, 40 polytetrafluoroethylene (PTFE) grafts with distal vein collar). As a result of this policy only 3 per cent of patients underwent primary amputation. At mean follow-up of 3 years, 64 vein-grafted limbs (72 per cent) and 20 PTFE-grafted limbs (50 per cent) remain viable, an overall limb salvage rate of 65 per cent. Graft patency is 72 per cent for vein grafts and 48 per cent for PTFE grafts. Following irreversible graft failure, major secondary amputation was required in all vein-grafted limbs and 94 per cent of PTFE-grafted limbs (overall 97 per cent limb loss following graft failure).

Recurrence of ipsilateral ischaemic symptoms warranting further intervention occurred in 38 vein-grafted patients (43 per cent), further vascular reconstruction was undertaken in 28 (74 per cent) of these patients and was successful in maintaining limb salvage to follow-up in 14 limbs. Following PTFE reconstruction, ipsilateral recurrence occurred in 25 patients (62 per cent) Revisional vascular surgery was undertaken in 20 of these limbs and was successful in seven patients.

Failure to intervene again after femorocrural graft failure would have resulted in loss of 21 salvageable legs, 25 per cent of all limbs saved by bypass to crural vessels. A reconstruction policy without femorocrural bypass (assuming 97 per cent limb loss) would have increased our primary amputation rate to 23 per cent, with loss of 81 salvageable limbs (24 per cent of limbs salvaged by all reconstructions). In conjunction with an increasing body of evidence showing poor outcome after vascular amputation we believe this work underlines the importance of femorocrural reconstruction, and an aggressive policy of reintervention following graft failure, in optimizing limb salvage rates

Lupus anticoagulant levels in patients with peripheral vascular disease

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Patients with lupus anticoagulant (LAC) and peripheral vascular disease have a high incidence of early graft thrombosis To assess the incidence of LAC, clotting parameters in 20 patients with claudication (group 1), 21 patients with critical ischaemia (group 2) and 16 patients before elective aortic aneurysm surgery (group 3) were studied and results compared with those from 20 general surgical controls.

Positive results for LAC by the dilute Russell's viper venom time (DRVVT) with the platelet neutralization procedure were present in 25 of 57 (44 per cent) of vascular patients compared with none of 20 general surgical cases. The three vascular groups showed a similar prevalence of LAC, and this differed very significantly from that in the controls. Of the 25 positive results only three were associated with an abnormal kaolin cephalin clotting time (which has previously been used as a marker for LAC). Fibrinogen levels were raised in seven of the 21 patients in group 2 but were normal in the remaining groups ($P = 0{\cdot}001$). The mean factor VII level (124·1 units dl^{-1}) in group 2 was higher than the mean of the remaining vascular patients (109·3 units dl^{-1}, $P < 0{\cdot}05$). There were no consistent abnormalities in protein C, protein S, antithrombin III, plasminogen, tissue plasminogen activator or plasminogen activator inhibitor I levels in any of the groups.

The incidence of LAC in patients with peripheral vascular disease and the potential risk of early graft thrombosis may justify routine testing by DRVVT before reconstructive vascular surgery and anticoagulation in those with an abnormal result

Natural history of carotid artery disease in high-risk patients

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A total of 150 patients with symptomatic peripheral vascular disease (PVD), 100 patients with symptomatic coronary artery disease (CAD), and 100 age- and sex-matched controls were examined prospectively for coexistent carotid artery disease by duplex scanning The incidence of >50 per cent carotid stenosis or occlusion was 33 per cent, 10 per cent and 3 per cent respectively. All patients were then entered into a natural history study to determine the subsequent incidence of transient ischaemic attack (TIA) and stroke

Questionnaires were sent to the patients' general practitioners after 1, 3 and 5 years, and all death certificates were examined. Follow-up data are available at 5 years for all but two patients (99·4 per cent). Seventeen per cent of patients with PVD and 13 per cent of those with CAD with carotid artery disease had a stroke within 5 years, compared with 6 per cent of controls ($P < 0{\cdot}001$ for PVD, P not significant for CAD). In 83 per cent of patients the stroke was ipsilateral to a >50 per cent carotid stenosis. The combined incidence of TIA and stroke was 37 per cent for PVD, 13 per cent for CAD and 11 per cent for controls ($P < 0{\cdot}01$ for PVD; P not significant for CAD) At entry, 13 of 50 (26 per cent) patients with PVD with carotid artery disease had cerebral symptoms and were successfully treated by carotid endarterectomy. Of the remaining 37 patients with PVD seven (19 per cent) became symptomatic on follow-up and a further five (14 per cent) underwent prophylactic carotid endarterectomy for >75 per cent stenosis.

These results indicate that patients with PVD undergoing elective surgery with coexistent carotid artery disease are at increased risk of subsequent TIA and stroke These patients need to be prospectively identified and considered for carotid endarterectomy where appropriate

Intraoperative B-mode scanning improves surgical technique but not immediate neurological outcome of carotid endarterectomy

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The successful outcome of carotid endarterectomy depends on meticulous operative technique. Intraoperative scanning with B-mode ultrasonography enables the vascular surgeon to identify technical imperfections immediately. Since 1986, this unit has used this technique to determine the adequacy of repair in 270 carotid operations. Of these, technical defects were identified in 13 patients, of whom nine underwent reparative surgery. Problems identified included intimal flaps in 11 and interarterial thrombus in two patients Four patients with minor intimal flaps judged to be insignificant did not undergo re-exploration. The frequency of operative defects detected by intraoperative scanning with the observed perioperative stroke rate per year is shown in the *Table* below. For comparison, operation-related strokes in 217 patients undergoing carotid endarterectomy in the 3-year period up to 1986 and introduction of intraoperative scanning are included.

Year	Technical defects by B-mode imaging	Total procedures	Perioperative stroke rate
1983	n a	81	3 (3·7)
1984	n.a.	74	4 (5·4)
1985	n.a.	62	3 (4·8)
1986	7	60	2 (3·3)
1987	4	47	2 (4·3)
1988	1	56	2 (3·6)
1989	1	50	1 (2·0)
1990	0	57	0 (0·0)

Values in parentheses are percentages. n.a., Not available

Indwelling shunts were used in six of 13 patients with defects compared with 40 of 257 patients without defects ($P < 0{\cdot}05$, χ^2 test). None of the patients with repaired or unrepaired intraluminal defects sustained an operation-related stroke, nor were there any late strokes In four patients with small unrepaired defects, no symptoms, carotid restenosis or flap visualization were subsequently noted. In addition, when disease of the common carotid artery was demonstrated by scanning, the endarterectomy was extended into this vessel Intraoperative B-mode scanning has decreased the frequency of intimal flaps and retained thrombus occurrence but has not decreased the incidence of perioperative stroke.

Topical lignocaine in carotid endarterectomy

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Carotid endarterectomy is now recognized as the treatment of choice for patients with severe carotid artery stenosis It has recently been suggested that the use of topical lignocaine before mobilization of the carotid bifurcation does not prevent associated wide fluctuations of pulse and blood pressure[1] This study was designed to assess the efficacy of topical lignocaine in this respect

Twenty-five patients, all with a history of transient ischaemic attacks and proven severe stenosis. underwent carotid endarterectomy under general anaesthesia Immediately before mobilization of the carotid bifurcation, 10 ml 1 per cent lignocaine ($n = 11$) or normal saline ($n = 14$) (random allocation) was used to immerse the vessels for 2 min Thereafter, a shunt was routinely inserted Measurements of pulse and blood pressure were recorded at 2-min intervals throughout the operation Mean values of pulse, systolic and mean blood pressure were calculated for each of the following periods. (1) initial dissection, (2) solution application, (3) after solution but before clamp, (4) clamp on to shunt insertion; (5) endarterectomy; (6) shunt removal to clamp off; (7) after reperfusion.

Pulse and blood pressure remained stable throughout the operation in the group receiving lignocaine, whereas marked fluctuations occurred in the placebo group. In particular, tachycardia and hypertension associated with clamp application during periods 4 and 6 in the placebo group were not seen in the group receiving lignocaine ($P < 0{\cdot}02$). During carotid endarterectomy under general anaesthesia, carotid sinus blockade with 1 per cent lignocaine abolishes potentially dangerous haemodynamic instability.

1. Barman AA, Moideen AS, Chaudhry SS, Ardell J, Barman SA, Cantu R. Nerve sparing dissection as alternative to anesthesia of carotid sinus nerve *Texas Heart Inst J* 1989; **16**· 107–9.

Role of bilateral transcranial Doppler ultrasonography in the preoperative assessment and peroperative monitoring of patients undergoing carotid endarterectomy

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Selective shunting in patients with inadequate cerebral perfusion following carotid clamping remains the ideal. Currently, transcranial Doppler ultrasonography appears to be the best simple intraoperative technique for monitoring cerebral perfusion

Thirty-six patients with symptomatic internal carotid artery stenosis of >70 per cent were examined. Preoperative ipsilateral common carotid artery compression was performed while a bilateral transcranial Doppler system was used to measure middle cerebral artery velocities (MCAVs). During operation, all patients were monitored using the same system.

On the ipsilateral side the mean (95 per cent confidence interval (c.i.)) change in MCAV during preoperative compression was 19·5 (9·5–29·5) $\mathrm{cm\,s^{-1}}$ and during operative clamping was 14·9 (5·6–24·2) $\mathrm{cm\,s^{-1}}$. There was good correlation between the changes in MCAV during compression and clamping ($r = 0{\cdot}85$). The contralateral side acted as a control and surprising changes were seen on occasions following carotid clamping.

The use of a Javid shunt was seen to restore cerebral perfusion in those who had reduced MCAV following clamping The mean (95 per cent c.i.) MCAV measurements on the ipsilateral side before clamping of 36·5 (29·3–43·6) $\mathrm{cm\,s^{-1}}$, correlated well with values after shunt insertion (37·5 (16·8–58·2) $\mathrm{cm\,s^{-1}}$); $r = 0{\cdot}75$.

Common carotid artery compression reproduces the effects of internal carotid artery clamping, and may prove to be a simple method of identifying patients who would benefit from a shunt during carotid endarterectomy

Breath-holding test: a simple measure of cerebral perfusion reserve, with a potential use in selecting patients for carotid endarterectomy

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Carotid endarterectomy is indicated for >70 per cent carotid stenosis However, selection of patients by degree of stenosis fails to take into account collateral supply that determines risk of stroke in the unoperated patient, and hence indication for endarterectomy. Cerebral perfusion reserve (CPR) is dependent on both the degree of stenosis and collateral supply. It can be estimated by measuring the increase in middle cerebral flow velocity (MCFV) occurring in response to the vasodilator carbon dioxide, and is reduced in patients with critical ischaemia. The test is limited by the requirement for a capnograph and/or supply of carbon dioxide.

A method requiring neither, in which the rise in carbon dioxide during breath-holding is used as the vasodilatory stimulus, has been developed The percentage increase in MCFV occurring during breath-holding per second is recorded. In 23 subjects undergoing carotid angiography the breath-holding method was compared with a conventional method in which the full range of vasodilation between hypocapnia (hyperventilation) and hypercapnia (carbon dioxide administration) was measured.

A good correlation between the two methods was found ($\rho = 0{\cdot}67$, $P < 0{\cdot}0001$), and both methods identified the same subjects as having abnormally reduced CPR This method was used to study CPR on the operated side of 16 patients before and after carotid endarterectomy. CPR increased from a mean of 0·71 per cent $\mathrm{s^{-1}}$ to 1·10 per cent $\mathrm{s^{-1}}$ ($P < 0{\cdot}004$, Wilcoxon signed rank test). In all nine patients in whom it was reduced below the normal range CPR returned to normal after operation ($P < 0{\cdot}001$).

It is likely that not only degree of stenosis but also CPR should be taken into account in selection of patients for endarterectomy The breath-holding method provides a simple and reliable measure of this.

Atherosclerotic plaques occur secondarily to removal of the arterial adventitia

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A new hypothesis, based on a rabbit carotid artery model, holds that arterial wall hypoxia, secondary to occlusion of the adventitial vasa vasorum, may initiate atherosclerotic plaque formation[1].

The anatomy of the carotid artery vasa vasorum of New Zealand White male rabbits was demonstrated by light and electron microscopy and by a new resin casting technique. Vasa vasorum remain adventitial and do not penetrate into the media. They arise directly from the main vessel lumen in addition to arterial branching points.

The adventitial layer (including all vasa vasorum) was surgically stripped from the left carotid artery of three groups of five anaesthetized rabbits. The right carotid artery (control) was simply mobilized.

At reoperation after 3 days no intimal proliferation was observed. After 7 days, a lesion with the characteristics of an early atherosclerotic plaque was seen, with no anatomical damage to the endothelium. Transmission electron microscopy confirmed smooth muscle cells and mononuclear leucocytes between the endothelium and the internal elastic lamina. After 14 days, a much broader lesion was evident. The mean(s.d.) intimal:medial ratio (assessed by computerized image analysis) of the control arteries ($n = 10$) was 0·038(0·005). After 7 days, the mean(s.d.) ratio was 0·21(0·062), $n = 5$ ($P < 0{\cdot}001$, Student's t test). After 14 days, the mean(s.d.) ratio was 0·46(0·18), $n = 5$ ($P < 0{\cdot}001$).

This study supports the hypothesis that damage to, or occlusion of, the vasa vasorum can cause intimal proliferation.

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Intraoperative streptokinase removes thrombus the balloon catheter cannot reach

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Intraoperative thrombolysis was performed on 31 acutely ischaemic legs following incomplete balloon catheter thromboembolectomy. There were 30 patients (16 men and 14 women) of median age 73 (range 43–82) years. The indications for operation were probable embolism in nine legs (group 1), probable thrombosis in 11 (group 2), graft occlusion in five (group 3) and iatrogenic thromboembolism in six (group 4). Sensomotor deficit was present in 25 legs and preoperative arteriography was obtained in only 16.

A total of 21 femoral, 11 popliteal and four graft thromboembolectomies were performed. Additional procedures included three fasciotomies, six angioplasties and six bypass grafts After passage of the balloon catheter, persistent distal thrombus/occlusion was demonstrated by operative arteriography A dose of 100 000 units streptokinase was then infused distally over a period of 30 min, and arteriography repeated. All patients received systemic perioperative heparin.

Results were assessed by the degree of arteriographic lysis, restoration of foot pulses and limb salvage at the time of discharge or death:

	Arteriographic lysis			
Group	Complete	Partial	Restoration of pulse	Limb salvage
1 ($n = 9$)	5	4	8	9
2 ($n = 11$)	4	4	3	7
3 ($n = 5$)	2	2	3	4
4 ($n = 6$)	0	2	0	3

There were five minor wound haematomas and seven deaths, none directly attributable to thrombolysis Coagulation studies showed no systemic effect.

In conclusion, operative arteriography is advisable after balloon catheter embolectomy to detect residual thrombus. Intraoperative streptokinase appears to be a safe and effective method of removing it

Intra-arterial thrombolytic therapy as a treatment for vascular graft occlusion

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Intra-arterial thrombolytic therapy (IATT) is becoming established as a valuable addition to the methods available for treating acute lower limb ischaemia Graft occlusion is an important cause of lower limb ischaemia and yet thrombolysis is not considered a suitable mode of treatment by most vascular surgeons[1]. Over a 3-year period 15 patients with 19 occluded grafts were treated with IATT for acutely ischaemic limbs (nine men, six women; mean age 63 (range 43–90) years). The agents employed were streptokinase in four of 19 (5000 units h^{-1}) and tissue plasminogen activator in 15 of 19 (0·5–1·0 mg h^{-1}) Ten patients received one infusion each, four patients had infusion on two separate admissions; one patient had four separate infusions during one admission Mean duration of ischaemia was 5·6 days (range 12 h–28 days). One Dacron (Du Pont) popliteal interposition graft and two Dacron bifurcated aortic grafts were treated The other 16 grafts were all femoropopliteal and included two non-reversed vein, one reversed vein, five polytetrafluoroethylene (PTFE) with Miller cuffs, seven PTFE alone and one Dacron. There were good results for 14 of 19 infusions and poor results for five, with one infusion stopped because of graft perforation The failures were either regrafted (four of five) or anticoagulated (one of five) Reconstruction has been required for six patients, between or after treatment episodes Four patients suffered complications, which included rethrombosis, local bleeding and graft perforation All but one patient who underwent below-knee amputation were discharged without limb loss, although one further patient has had an above-knee amputation at another institution In our experience, unlike that of other centres, thrombosed Dacron grafts have been successfully treated without problems. These results suggest that Dacron graft failure is a suitable indication for thrombolysis

1 Earnshaw JJ, Shaw JFL. Survey of the use of thrombolysis for acute limb ischaemia in the UK and Ireland. *Br J Surg* 1990, **77** 1041–2

Peroperative tissue plasminogen activator thrombolysis as an adjunct to surgery

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Intra-arterial fibrinolytic therapy with streptokinase has been used as an alternative and as an adjunct to catheter embolectomy, but long infusion times and systemic bleeding have limited its application. Because tissue plasminogen activator (tPA) causes more rapid thrombolysis than streptokinase and has a shorter half-life, intra-arterial bolus administration is safer and more controlled[1]

When embolectomy fails to remove distal thrombus, bolus intra-arterial administration of tPA may be used to lyse any remaining clot lying in inaccessible vessels. This approach has now been used successfully in six patients, five with peripheral arterial emboli and one with a blocked vascular graft. In all cases, two bolus injections of tPA (10 mg) at 10-min intervals have resulted in complete lysis of remaining clot as demonstrated by arteriography. There have been no associated bleeding problems and we conclude that tPA is a relatively safe and reliable adjunct to surgery in the treatment of occluded distal blood vessels.

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Long-term results of intra-arterial thrombolysis

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Intra-arterial thrombolysis (IAT) was planned in 104 patients with acute, subacute or chronic ischaemia. In all, 97 patients received IAT on 109 occasions, streptokinase in 92, tissue plasminogen activator (tPA) in 17 The mean age at presentation was 68 years, 75 per cent were men Rest pain occurred in 55 per cent of patients, 66 per cent of these (compared with 16 per cent of patients with claudication) were treated within 1 week of onset of symptoms. Half of the patients had femoral and 25 per cent popliteal occlusions, 15 per cent had occluded grafts.

Complete lysis, as determined radiologically, was achieved in 54 per cent of cases, and partial lysis in 18 per cent. Patients with rest pain were treated as effectively as those with claudication Lysis was more effective the earlier it was used Following complete lysis 24 patients required no further treatment, 15 underwent percutaneous transluminal angioplasty, and 12 surgical reconstruction Patency 1 year after treatment, as determined by life-table analysis, was 58 per cent. There was no significant difference between the three groups. Of those patients undergoing partial lysis, ten were improved clinically However, overall only three of these patients were asymptomatic on discharge from hospital. Intra-arterial thrombolysis was successful in completely clearing approximately half the cases attempted, of these half remained patent at 1 year.

Anticoagulant effects of aprotinin

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Bleeding remains a troublesome complication of surgery and is an important factor in morbidity and mortality. The serine protease inhibitor aprotinin significantly reduces transfusion requirements during open heart surgery Whether this benefit is associated with an increased tendency to thrombosis has not been studied The effect of aprotinin in a new experimental arterial thrombosis model was investigated.

In experiment 1, the infrarenal aorta in 17 male Sprague–Dawley rats was replaced with a 1·0-mm diameter polytetrafluoroethylene tube graft of varying lengths. The mean(s.d.) time of graft occlusion, recorded by palpation, Doppler ultrasonography and the milking test, was 20·2(1·8), 35·8(6·1) and 43·7(6·6) min for grafts of 10, 7·5 and 5·0 mm, respectively ($r = 0{\cdot}86$, $P < 0{\cdot}05$).

Using this model the effects on thrombosis of intravenous aprotinin (4 mg kg^{-1} loading dose and 1 mg $\mathrm{kg}^{-1}\,\mathrm{h}^{-1}$ infusion) and heparin (100 units kg^{-1} intravenous loading dose and 15 units $\mathrm{kg}^{-1}\,\mathrm{h}^{-1}$ infusion) singly and in combination were studied. Prothrombin time was measured. Results were

Group ($n = 6$)	Graft length (mm)	Time to thrombosis (min)	Prothrombin time (s)
Control	10	20·2(1·8)	21·9(3·0)
Aprotinin	10	71·7(20·4)*	26·4(6·2)*
Heparin	10	118·3(26·4)*†	37·4(8·0)*
Aprotinin plus heparin	10	109·5(15·2)*	39·9(14·5)*

Values are mean(s.d.) $^*P < 0{\cdot}05$ *versus* control, $^†P < 0{\cdot}05$ *versus* aprotinin

In summary, a new, simple and reliable experimental arterial thrombosis model has been developed Aprotinin has an anticoagulant effect in this model The simultaneous infusion of heparin and aprotinin does not have an additive effect. We speculate that aprotinin may be the ideal agent for anticoagulation in surgery.

Pathophysiology of vibration white finger: effect of obliterative arterial lesions

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The pathogenic significance of organic vessel disease in the digits of patients with vibration white finger (VWF) is unclear as conflicting evidence demonstrates maximal hyperaemic blood flow in the digits of this group[1]. Using $^{99\mathrm{m}}$Tc-radiolabelled human serum albumin and a γ camera, hyperaemic blood flow in the hands of 44 patients with VWF was measured. Perfusion defects can be visualized by recording summated views of radioactivity 30 s after release of an occluding pneumatic cuff Absence of radioactivity indicates vessel stenosis. A simple scoring system applied to the image of each hand objectively documented obliterative vessel disease; each hand could score a maximum of 12 points.

	Blood flow (ml per 100 ml tissue per min)*	Score
Right hand ($n = 44$)	23·9 (5·7–43·8)	8 (0–12)
Left hand ($n = 44$)	22·3 (7·4–41·8)	7 (0–12)

Values are median (range). *Normal hand blood flow >25 ml per 100 ml tissue per min

These results demonstrate a significant correlation between score and hyperaemic hand blood flow ($r_S = 0{\cdot}71$, $P < 0{\cdot}001$) Moreover, the summated views detected perfusion defects in 13 per cent of hands which otherwise had a normal hyperaemic blood flow.

By combining both methods obliterative lesions were seen in one or more digits in /4 per cent of the hands examined. We conclude that organic vessel disease is of pathophysiological significance in the aetiology of VWF and that a combination of summated isotope images and hyperaemic hand blood flow measurement gives a sensitive method for assessing arterial perfusion defects This may be important for medicolegal purposes.

1. Ekenvall L, Lindblad L, Bevegard S. High vascular tone but no obliterative lesions in vibration white fingers. *Am J Ind Med* 1987, **12**: 47–54.

Altered haemorrheological properties in Raynaud's disease: a possible pathogenic mechanism

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The pathogenic mechanism of vasospasm in primary Raynaud's disease remains unclear Fluctuations in female sex hormones have been associated with altered digital blood flow and changes in haemorrheological parameters. This study therefore assessed cold sensitivity in 14 women with Raynaud's disease and 11 control subjects during menstruation when both circulating oestradiol and progesterone levels are low. All patients underwent a cold stress test by challenging them to a period of total body cooling and resting, the recovering blood flow was measured using venous occlusion strain-gauge plethysmography Red cell deformability was measured in 13 patients with Raynaud's disease and ten controls using the St George's Filtrometer (Carri Med). Whole blood, devoid of platelet aggregates and white blood cells, was filtered through 5-μm pore Nucleopore membranes in phosphate-buffered saline. The clogging particles (CP) and red cell transit times (RCTT) were calculated.

	Raynaud's disease	Controls
CP ($\times 10^5$)	2·92 (2·0–9·78)*	2·53 (1·46–6·22)
RCTT	12·59 (11·49–14·89)*	11·84 (10·5–14·15)
Resting blood flow (ml 100 ml^{-1} min^{-1})	16·86 (1–54·1)†	31·72 (3·2–65·2)
Recovery blood flow (ml 100 ml^{-1} min^{-1})	10·89 (0·5–34·3)†	19·22 (3–60·4)

Values are median (range). *$P < 0{\cdot}05$; †$P < 0{\cdot}01$ (Mann–Whitney *U* test)

Subjects with Raynaud's disease have significantly fewer deformable red blood cells during menstruation and are also significantly less cold tolerant when compared with controls. Moreover, there was an inverse relationship with CP and recovery from a cold stress test with Raynaud's disease ($r_S = -0{\cdot}61$, $P < 0{\cdot}05$). We conclude that heightened cold sensitivity in women with Raynaud's disease during menstruation may be partially explained by reduced red cell deformability

Endothelial cell injury in the risk factors of atherosclerosis

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Hypercholesterolaemia and hypertension may promote atherosclerosis through endothelial injury Using von Willebrand factor antigen (vWFAg) as a specific marker of endothelial cell damage, this study investigated whether patients with hypertension or hyperlipidaemia exhibited evidence of endothelial injury, as detected by raised vWFAg levels

Cholesterol, triglycerides, high-density lipoprotein C, systolic and diastolic blood pressures and vWFAg were measured in 28 patients with familial hypercholesterolaemia, 17 with polygenic hypercholesterolaemia, 35 with hypertension and an equal number of age- and sex-matched hospital staff. None had symptomatic vascular disease; hypertension was defined as systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg.

Mean(s.d.) vWFAg levels were significantly higher in polygenic than in familial hypercholesterolaemic subjects, at 125(35) and 108(36) units dl^{-1} respectively ($P < 0{\cdot}05$, Mann–Whitney *U* test), with both higher than their respective controls of 90(27) units dl^{-1} ($P < 0{\cdot}001$ and $P < 0{\cdot}05$, respectively). The highest levels of vWFAg were found in hypertension, at 138(33) units dl^{-1} ($P < 0{\cdot}0001$). Despite this striking elevation in vWFAg levels in patients with hypercholesterolaemia, there was no correlation between vWFAg and cholesterol concentrations in either familial or polygenic hypercholesterolaemia. There was a significant correlation with systolic blood pressure in patients with hypertension ($r_s = 0{\cdot}46$, $P < 0{\cdot}01$).

These results demonstrate a clear association between increased serum vWFAg levels and risk factors for atherosclerosis Both hypercholesterolaemia and hypertension may promote endothelial injury.

Percutaneous transluminal angioplasty: an effective treatment for infrainguinal vein graft stenoses

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Since July 1988 83 infrainguinal vein grafts have been performed at this institution, of which 15 (18 per cent) occluded within 1 month. The remaining 68 grafts have been monitored in a graft surveillance programme with exercise ankle brachial pressure indices and duplex scanning at 1, 3, 6, 9 and 12 months and subsequent 6-monthly intervals after operation. All stenoses detected by duplex scanning were confirmed by angiography and treated by percutaneous transluminal angioplasty (PTA).

To date, 23 grafts (34 per cent) have developed 24 stenoses. The majority (63 per cent) of these stenoses have occurred within 6 months of surgery Twenty-one stenoses (88 per cent) have been successfully treated by PTA The median follow-up after PTA is 18 (range 4–31) months. Duplex surveillance of 20 of these successful cases showed that although the angioplasty site initially demonstrated turbulent flow, by 1 month this had resolved and the site appeared normal. Three angioplasties (13 per cent) were unsuccessful (persistent duplex velocity increase after PTA) and were treated by revisional surgery.

Two grafts have occluded during the period of the graft surveillance and PTA programme. One patient who failed to attend for graft surveillance presented with a graft occlusion that was treated by fibrinolysis and PTA of a distal graft stenosis. The second patient was known to have a graft stenosis but did not undergo angioplasty because of cholesterol emboli present during preoperative angiography. This graft was salvaged by fibrinolysis and revisional surgery.

In conclusion, we have found PTA to be a highly effective treatment for infrainguinal vein graft stenoses, with 88 per cent of angioplastied grafts appearing normal on duplex scanning at a median of 18 months after PTA.

Inhibition of angiotensin-converting enzyme reduces intimal hyperplasia in experimental vein grafts

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Intimal hyperplasia is an important factor in the pathophysiology of vein graft failure. Local renin–angiotensin systems have been implicated in the development of intimal hyperplasia in de-endothelialized arteries. The effect of angiotensin-converting enzyme (ACE) inhibition on the development of intimal hyperplasia in experimental vein grafts was examined in this study. Ten rabbits received captopril (10 mg kg^{-1}) daily orally; 1 week later the right carotid artery was divided and bypassed with the right external jugular vein in these rabbits and in ten controls. Captopril was continued for a further 28 days, when the grafts were harvested. Intimal hyperplasia in the proximal, middle and distal segments of five perfusion-fixed grafts from each group was determined. The remaining grafts were studied *in vitro*, and their responses to noradrenaline, histamine, serotonin, angiotensin I and angiotensin II examined.

The intimal thickness in all segments of the experimental group was significantly less than that of the control group as shown in the *Table* below.

	Intimal thickness (μm)		
	Control group	Experimental group	P
Proximal	156(5·1)	90(4·3)	<0·0001
Middle	150(8·3)	95(5·3)	<0·0001
Distal	151(7·3)	88(2·7)	<0·0001

Values are mean(s.e.m.)

The experimental group were hypersensitive to serotonin (mean(s.e.m.) ED$_{50}$ 1·1(0·2) × 10^{-6} M in the control group *versus* 5·5(0·5) × 10^{-7} M in the experimental group, $P < 0·005$). The maximal response to serotonin was reduced, from 1·6(0·3) mg in the control group to 0·8(0·14) mg in the experimental group ($P < 0·05$). The maximal response to angiotensin I was also significantly reduced, from 0·47(0·06) g in the control group to 0·2(0·05) g in the experimental group ($P < 0·02$). These results suggest that ACE is involved in the modulation of vein graft intimal hyperplasia. ACE inhibition may also affect the vasomotor responses of vein grafts. Therefore ACE inhibitors may have therapeutic applications in patients undergoing vein bypass procedures.

High saphenous ligation for lower limb varicosities preserves a useful long saphenous vein

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There is controversy over the surgical management of varicose veins, stripping of the long saphenous vein (LSV) may provide superior results to high ligation. However, preservation of the LSV is desirable for future coronary or peripheral artery bypass. A total of 75 limbs in 44 patients were studied, following high saphenous ligation with multiple stab avulsions. Subjective and objective assessment of surgery was made using a linear analogue score. Patency, length and diameter of the LSV 12 (range 5–14) months after operation were measured using a Toshiba SPA270A duplex scanner and a Diasonics colour flow scanner. Valvular incompetence in the LSV and perforators was measured.

Results show a good subjective and objective outcome in 95 per cent and 97 per cent of patients respectively. The LSVs were patent from groin to knee in 82 per cent and from groin to ankle in 68 per cent, with a mean diameter of 4 (range 3–5) mm. There was no association between the presence of reflux in the LSV and relief of symptoms ($\chi^2 = 0·10$, P not significant) or objective ($\chi^2 = 0·07$, P not significant) and subjective ($\chi^2 = 0·83$, P not significant) cosmetic result.

It is concluded that high ligation of the LSV preserves the LSV for future use with good symptomatic and cosmetic results.

Long-term follow-up treatment for varicose veins

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In one clinic 363 legs were treated for varicose veins, by surgery or by compression sclerotherapy, and were followed up for a minimum of 5 years (mean 9 years 2 months). Patients were treated by injection sclerotherapy if there was no evidence of long or short saphenous reflux and the varicosities were confined to below the knee. All patients were seen at 1-year intervals and success of treatment determined by a standardized questionnaire and examination.

Patients treated by disconnection of the saphenofemoral junction and stripping with or without local ties had the highest proportion of success (91 per cent) at the end of follow-up, although 28 per cent of these patients required further procedures during the follow-up period. Similar patients, whose long saphenous vein was not stripped, had an 84 per cent final success rate, but 43 per cent had required further treatment during follow-up.

At presentation 28 per cent of patients were judged suitable for sclerotherapy alone, but in only 55 per cent of these was such a procedure deemed to be successful at follow-up in the absence of subsequent treatment. A further 27 per cent of patients had a satisfactory result after a later surgical procedure.

Several conclusions can be drawn from a detailed analysis of this long-term follow-up, perhaps the most important is that the selection of patients for sclerotherapy alone has to be even stricter than it was in this series.

Venous pump function after ankle fractures

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Trauma to calf veins after lower limb fracture impairs venous outflow and delays return of normal limb function. Calf venous muscle pump function in the fractured limb may also be relevant. Air plethysmography (APG) was used to assess calf venous pump function after ankle fracture – where direct venous injury is minimal. After internal fixation of 18 ankle fractures, a duplex scan was performed to rule out venous obstruction, and APG was used to measure calf venous volume (CVV), rate of venous filling (VFI), and the venous volume changes produced by calf muscle contraction, i.e. ejection volume fraction (EVF) and residual volume fraction (RVF) in both fractured and contralateral (control) limbs. Duplex scanning and APG were repeated after immobilization of the injured leg in a below-knee cast for 6 weeks. All duplex scans were normal. APG results were

	Immediate		After 6 weeks	
	Control	Fracture	Control	Fracture
CVV (ml)	86·8(32·7)	113·4(31·1)	55·4(34·7)	65·4(42·0)
VFI (ml s^{-1})	2·26(1·90)	2·89(3·0)	0·69(0·60)	1·06(0·87)
EVF (%)	58·4(34·7)	14·7(9·0)*	37·3(25·8)	23·2(25·2)
RVF (%)	43·4(25·8)	87·5(12·1)*	41·3(27·5)	61·9(38·6)†

Values are mean(s.d.) *$P < 0·0005$, †$P < 0·02$ *versus* control (Student's t test)

These data demonstrate that after internal fixation of ankle fractures there is a significant reduction in calf venous pump function, which has improved at 6 weeks but still remains significantly below normal. These changes may contribute to the delay in return of normal limb function after fracture.

Reliability of duplex scanning in the measurement of lower limb venous blood flow

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Duplex scanning may be used to quantify venous reflux in individual veins of the lower limb, although these measurements are difficult to reproduce accurately.

This study attempted to assess the reliability of venous blood flow measurements, made by a single experienced operator, by duplex scanning *in vivo* in the long saphenous (LSV), short saphenous (SSV), common femoral (CFV), and popliteal (PV) veins by an analysis of the variation of repeated measurements in the same vein. Vessel diameter and blood velocity measurements (forward and reflux peak, mean, and time-averaged velocity) were made in the above veins in limbs with venous reflux after a standard calf compression, 66 readings in 33 limbs in the LSV, 30 readings in 15 limbs in the SSV, 20 readings in ten limbs in the PV and 14 readings in seven limbs in the CFV were taken.

The variance components of these measurements due to variability between legs (s_B^2) and to measurement error within legs (s_W^2) was calculated and the reliability (r) of a measurement calculated from the equation:

$$r = 1/[(1 + s_W^2)/(n \times s_B^2)]$$

where n is the number of readings taken[1]

The duration of flow and vessel diameter are measurable precisely in all veins if two or more readings are taken ($r > 90$ per cent), but velocity measurements are less precise with a range of r between 61 per cent for reflux peak velocity in the SSV and 98 per cent for the mean velocity at peak reflux in the PV Further studies are now in progress to assess the reliability of these measurements between individual operators

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Oxygen-derived free radicals and ischaemia–reperfusion in venous ulceration

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The aetiology of venous ulceration remains keenly disputed To examine the hypothesis that ischaemia develops on dependency with reperfusion on elevation, thromboxane production and neutrophil superoxide release were investigated in patients with venous ulceration.

Blood was sampled in nine patients at the following intervals: after 30 min lying supine, after a subsequent 30 min of leg dependency, and then after a further 30 min of re-elevation; and at the same intervals in six patients who remained supine throughout. Plasma thromboxane B_2 (TxB_2) levels were measured using an enzyme immunoassay, and neutrophil superoxide production was determined by a colorimetric cytochrome *c* assay

Mean(s.e.m.) TxB_2 levels did not vary significantly with time in controls and fell from 29·2(8·3) to 20·2(2·7) pg ml^{-1} at 90 min. In test subjects, TxB_2 rose from 25·2(4·4) at rest to 58·7(12·4) pg ml^{-1} on dependency, and increased further to 107·6(37·4) pg ml^{-1} on re-elevation ($P < 0{\cdot}05$, Wilcoxon signed rank test) Mean(s.e.m.) neutrophil superoxide release did not vary with time in controls, but rose from an initial 1·52(0·23) to 2·57(0·42) nmol per min per 10^6 neutrophils during dependency, and remained raised at 2·10(0·55) nmol per min per 10^6 neutrophils on re-elevation ($P < 0{\cdot}05$). These changes in dependent patients were significantly different from those in controls ($P < 0{\cdot}05$, Mann–Whitney U test).

Thromboxane was generated both during dependency and on re-elevation. This response, with the liberation of oxygen-derived free radicals, is typical of an ischaemia and reperfusion injury, which if repeated continously may be important in the aetiology of venous ulceration.

Value of liquid crystal thermography and duplex scanning in diagnosis of deep vein thrombosis

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It has been shown that deep vein thrombosis (DVT) can be detected by duplex scanning with a sensitivity of 97 per cent and specificity of 94 per cent, and by liquid crystal thermography (LCT) with a sensitivity of 97 per cent and specificity of 62 per cent.

The aim of this study was to demonstrate that by using LCT, duplex scanning and venography (VNG) can be avoided in the majority of patients suspected of having DVT

A total of 100 patients with suspected DVT were studied; 98 had all three tests, and the results are summarized below:

	Duplex scan		LCT*	
	DVT	No DVT	Positive	Negative
DVT on VNG	43 (93)	3	42 (93)	3†
No DVT on VNG	5	49 (91)	15	38 (72)

Values in parentheses are percentages. *LCT not available for two patients, †two patients had the symptoms for more than 10 days. One patient had a small calf DVT, missed also on duplex scanning

The results compared with VNG give a sensitivity of 93 per cent and a specificity of 91 per cent for the duplex scan, and 93 per cent and 72 per cent for LCT, respectively.

We conclude that the high negative predictive value of thermography, 38 of 41 (93 per cent) (or if performed within 1 week from the presentation of symptoms 40 of 41 (98 per cent)), makes duplex scanning unnecessary in the presence of a negative LCT test This practice would have saved 38 patients from undergoing duplex scanning at the expense of missing one calf thrombus. Furthermore, the combination of LCT and duplex scanning gave the correct answer to whether to treat or not in the majority of patients, and a venogram was needed in only six (6 per cent) patients.

Low molecular weight heparin in the prevention of recurrent venous thromboembolism

S.K. Das, N.V. Wilson, N.J. Standfield and V.V. Kakkar, *Thrombosis Research Institute, London, UK*

A study was undertaken to find out whether low molecular weight heparin (LMWH) could be used as an alternative to warfarin therapy One hundred consecutive patients suffering from phlebographically proven acute deep vein thrombosis (DVT) were randomly allocated to receive over a 3-month period a fixed self-administered daily dose of 5000 units LMWH or warfarin (the dose of which was regulated to maintain a prothrombin index of twice the control value)

Patients were reviewed at 4-week intervals to assess compliance with the treatment, monitor side-effects and document evidence of recurrence. Repeat phlebography was performed at the end of the study period, or earlier if symptoms developed, to document evidence of recurrence. The cost-effectiveness of each treatment was estimated by economic analysis, taking into account the number of visits required to hospital for monitoring and the need for hospitalization due to complications of therapy. Results were analysed according to intention to treat. Of 100 patients five developed phlebographically proven recurrent DVT, three in the group receiving LMWH and two in those receiving warfarin. None of the 50 patients on LMWH developed any side-effects to the treatment, but five of the 50 patients being treated with warfarin developed haemorrhagic and allergic complications; three of these required hospitalization for further treatment. Cost analysis of the two methods of treatment indicated that use of LMWH could produce savings of approximately £500 per patient

In conclusion, the adjusted dose of warfarin therapy and a fixed daily dose of LMWH are equally effective in preventing recurrence in DVT. However, warfarin therapy, in spite of strict laboratory control, is associated with more frequent side-effects and appears to be more expensive

Thrombolytic treatment and post-thrombotic syndrome

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The ideal form of treatment for acute deep vein thrombosis in order to prevent post-thrombotic syndrome remains controversial Thrombectomy, although very effective, is rarely performed because of associated complications and poor long-term results. Thrombolytic treatment has been claimed to be the alternative option. Thirty patients treated with either heparin alone or by thrombolytic treatment 12 years ago were followed up at a 5-year interval. The incidence of post-thrombotic syndrome in this study population was analysed.

Clinical changes due to post-thrombotic syndrome were assessed on an analogue scale. Haemodynamic changes in the venous system were evaluated by foot volumetry and colour duplex ultrasonography. Microcirculatory changes in the lower limb were assessed by measurement of transcutaneous oxygen pressure and laser Doppler blood flow. Changes in the fibrinolytic parameters were compared between groups.

The assessment 12 years after the initial treatment suggests that there is progressive deterioration of the limb, in the development of post-thrombotic syndrome, irrespective of the nature of the treatment and location of initial thrombi. There appears to be a paralysis of venoarterial response in the treated limbs, and reduced oxygen diffusion, which is said to be responsible for development of venous ulcer, however, the changes in the microcirculation do not appear significantly different in either group. Similarly, there was no demonstrable difference in the changes in any of the parameters concerned with systemic fibrinolysis.

It may therefore be concluded from the long-term prospective study that thrombolytic treatment does not confer any particular advantage over heparin therapy in the prevention of post-thrombotic syndrome.

Ambulatory intermittent pneumatic compression for the treatment of lower limb oedema: early clinical results

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Ambulatory intermittent compression is the ideal treatment for lower limb oedema. A pneumatic boot has been developed that produces intermittent calf compression while walking. In this pilot study the effectiveness of this boot in the maintenance of limb volume reduction in ten patients with chronic lymphoedema was assessed.

The boot comprises four pneumatic air cells; two plantar ones communicating with an upper and lower calf cell. During walking sequential calf compression is achieved, producing an interface pressure at the calf of 35–50 mmHg with a resting pressure of 20 mmHg. Ten patients with chronic lymphoedema of a mean duration of 5 years with a mean limb volume (measured to 30 cm above the medial malleolus) of 4020 ml underwent intensive inpatient Flowtron treatment for 1 week and were then established on maintenance Flowtron treatment at home for 20 weeks followed by 20 weeks of ambulatory intermittent compression. Limb volumes were assessed fortnightly by water displacement.

The mean reduction in limb volume after 1 week inpatient treatment was 8·5 per cent. Home Flowtron treatment effectively maintained limb volume reduction, no significant increase in limb volume being seen over the 20-week treatment period. Limb volume reduction was also maintained by the ambulatory boot but without the necessity for patients to be immobilized. Most patients found the boot comfortable and easy to manage.

In patients with chronic lymphoedema the ambulatory intermittent compression boot is as effective in maintaining limb volume reduction as home Flowtron treatment and is comfortable and convenient. Early studies suggest that the boot may also have a role to play in the treatment of chronic venous insufficiency.

This study was sponsored by the British Heart Foundation

Comparative vascular audit using the POSSUM scoring system

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The use of overall mortality and morbidity figures to compare the performance of different surgical units can be misleading, as they take no account of variations in surgical procedure and patient fitness. To examine these effects the outcomes from vascular surgery in two hospitals during a similar 9-month period have been compared using the POSSUM scoring system[1]. In unit 1 a total of 255 patients underwent vascular surgery with an operative mortality rate of 9·4 per cent and morbidity rate of 37·3 per cent. In unit 2 a total of 89 patients underwent vascular procedures with an operative mortality rate of 20·2 per cent and morbidity rate of 47·2 per cent. At first sight the differences in operative result between the two units appear to be significant. However, analysis using the POSSUM system predicts a mortality rate of 10·2 per cent for unit 1 and 20·2 per cent for unit 2 (with morbidity rates of 38·4 per cent for unit 1 and 50·6 per cent for unit 2). Receiver operating curve (ROC) analysis demonstrated no significant difference between the two units (*Table*). POSSUM analysis may be of use in comparative audit.

	Mortality		Morbidity	
	Unit 1	Unit 2	Unit 1	Unit 2
Area under ROC	0·878	0·918	0·756	0·795
Standard error	0·046	0·042	0·033	0·048

1. Copeland GP, Jones D, Walters M. POSSUM. a scoring system for surgical audit. *Br J Surg* 1991; **78**: 355–60.

Correspondence

Surgical training in the UK

Sir

At the Annual General Meeting of Fellows of the Royal College of Surgeons of England on 14 November 1991 the motion 'This House believes that the time has come to introduce a residency training programme' was carried unanimously. During the preceding debate it was apparent that there is general dissatisfaction with the current state of surgical training in the UK.

The Association of Surgeons in Training hopes that the Royal College of Surgeons of England acts on the wishes of their Fellows with vigour similar to that applied by the College to the introduction of the new examination structure, despite opposition from the Fellows on that issue when it was debated at the 1988 AGM[1] At that time the Association of Surgeons in Training stated that these changes should be linked to changes in career structure[2] This has not happened. Indeed, many general surgeons in their late 30s are now compelled to take the new intercollegiate examination irrespective of length of previous training or success at the 'old' FRCS All surgeons appointed to numbered higher surgical training (i e. senior registrar) posts on or after 1 January 1991 are required to pass the intercollegiate examination before accreditation will be granted.

The Association of Surgeons in Training sees the following as minimum requirements for the introduction of residency training programmes·

1 Full implementation of the process of selection for higher surgical training at the career registrar stage, rather than at senior registrar appointment
2. Integration of research into higher surgical training, rather than selection for training based on prior acquisition of a higher degree by thesis.
3 A process of monitoring of training that is directed at the individual rather than the current post- and hospital-orientated review. This is vital if surgical training is to be shortened from the current 12–14 years to about 8 years

These changes should occur in parallel rather than in series, and start soon. They must be underpinned by a sustained increase of 2 per cent per annum in the number of consultant surgeons in all specialties as specified in 'Achieving a balance'[3]. Finally, we must be certain that the interval between the completion of basic surgical training and acceptance on to residency training programmes does not become the time when surgical trainees continue to be overexperienced and undertrained.

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3 Hospital medical staffing – achieving a balance. Consultative document issued on behalf of the UK Health Departments, the Joint Consultants Committee, and Chairmen of the Regional Health Authorities. July, 1986.

Reply from the President of the Royal College of Surgeons of England

Sir

The Royal College of Surgeons of England is firmly committed to a more structured approach to the planning and supervision of both basic and higher surgical training.

The purpose of basic surgical training (BST) is to ensure that trainees acquire a sound knowledge of the applied basic sciences relevant to surgery, and of that core knowledge and experience in the generality of surgery which is important for any surgical specialist to have Considerable progress has been made recently in establishing good SHO rotations which provide trainees both with the necessary range of experience and also with a greater degree of security than has in the past been the case The broad nature of this stage of surgical training, which is now all conducted at SHO level, is reflected in the criteria for entry and revised content of the new FRCS examination, which in future the English College would like to see called the MRCS.

Higher surgical training (HST) starts with appointment to a career registrar post, at which time the trainee should be enrolled and numbered by the relevant specialist advisory committee (SAC) This has now become the most important step in the surgical career ladder and trainees will remain in the SHO grade until it has been achieved

Two distinct phases of HST are beginning to emerge The first could be called 'general specialty training', leading to accreditation by the SAC; the second 'advanced surgical training', in which the now accredited trainee gains further experience and training in a subspecialty of his or her choice.

Given such a distinction in the stages of training towards consultant practice, the structure of a model 6-year HST programme would be 4 years of general specialty training, including 1 year of research if this had not already been achieved, followed by acquisition of the intercollegiate specialty examination and accreditation. There would then follow approximately 2 years of advanced training, without the prospect of further certification and during which the trainee prepared himself or herself for a consultant post offering the subspecialty of his or her interest

As such structured HST programmes are developed, it is possible to envisage the abolition of the present barrier between career and senior registrar, so that HST becomes a graded continuum of increasing responsibility as consultant status is approached.

One requirement for such a scheme is that the number of career registrar and senior registrar trainees should be approximately in balance. In most surgical specialties this is approaching more quickly than many would have foreseen. Another important consideration is the acknowledgement of the over-riding importance of the career registrar appointment and the need to develop an agreed and accepted method of regular assessment during HST, probably including a formal contractual review after completion of the first year of the programme

I would like, therefore, to reassure the President and Secretary of ASIT that the English College is committed to the principles outlined in their letter and that the College is working with the other interested parties, such as the JCHST, to develop a more structured approach to the whole of surgical training. This, we believe, will result in more appropriate and comprehensive training being achieved in a shorter period of time. We would not, however, wish to compromise over the need for all specialist surgeons to have a proper grounding in the principles of surgery in general, which we believe is one of the current strengths of surgical training in the UK

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Mirizzi syndrome in a patient with carcinoma of the gallbladder

Sir

We read with interest the article by Baer *et al.* (*Br J Surg* 1990; 77· 743–5) on the management strategy of Mirizzi syndrome. We see a number of relatively young patients with gallbladder cancer and had reason to operate on a 45-year-old woman referred with fundal gallbladder cancer infiltrating the liver and obstructive jaundice due to stones in the common bile duct. The patient had had a cholecystostomy and biopsy before referral

During the extended cholecystectomy and wedge resection of the liver it became apparent that the patient had a grade II Mirizzi syndrome. The nature of the pathology precluded a cholecystocholedochoduodenostomy and the fistulous track was oversewn and a transduodenal sphincteroplasty was performed to clear and decompress the common bile duct. The cholecystostomy track was excised. The patient developed a small biliary leak from the liver bed which cleared spontaneously.

Given the premise that a Mirizzi syndrome follows long-standing gallstone disease[1,2] and that gallbladder cancer may share the same aetiology[3,4], both conditions may coexist. An endoscopic or percutaneous biliary aspirate examined cytologically in established cases of Mirizzi syndrome may give the diagnosis of gallbladder cancer before operation and help avoid unnecessary operations in selected patients.

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Surgical management of the thoracic outlet compression syndrome

Sir

We read with interest the paper by Davies *et al.* (*Br J Surg* 1991, **78**: 1193–5) reviewing their surgical management of the thoracic outlet compression syndrome (TOCS). We have recently audited 30 consecutive patients with the neurological variety of TOCS who have been surgically treated by one of us (A. J. L.) in the period May 1986 to October 1989.

Most were referred by other consultants: orthopaedic, 14 patients; rheumatology, 13, general surgery, one, and only two patients directly by general practitioners. The female : male ratio was 3 : 1 and of the 22 women four required bilateral surgery. Most patients (22 of 30) had had symptoms for over a year. Symptoms were considered as motor (arm weakness, undue fatiguability, muscle ache), sensory (proximal pain, paraesthesia, distal numbness) or vasomotor (Raynaud's phenomenon, cold, pallor, blue). Nine patients had symptoms from all three groups, nine had sensory and motor symptoms; six had sensory symptoms alone, and one had motor and vasomotor symptoms. Five had sensory and vasomotor symptoms.

In all 34 operations a supraclavicular approach was used and the first rib excised. A musculotendinous band was divided in 20 patients, scalenus medius divided in 14, a cervical rib resected in 12 and levator pleurae divided in three. Post fixation of the brachial plexus was noted in three patients.

Early complications included infraclavicular anaesthesia in seven patients, the pleura holed in six and a frozen shoulder in one.

Of the 14 patients who were symptom-free at 6 weeks, 13 remained so at 1 year, the other reporting continued improvement. Nineteen reported symptomatic improvement at 6 weeks of whom four became symptom-free at 1 year and four reverted to their original severity of symptoms. One patient reported no improvement at 6 weeks and 1 year. No patients were made worse by the operation.

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Prevalence, development and management of abdominal aortic aneurysms

Sir

The conclusion drawn by Scott *et al* (*Br J Surg* 1991, **78**: 1122–5) that under 10 per cent of patients with ultrasonographically detected abdominal aortic aneurysm (AAA) require surgery with follow-up is not supported by the data using their strict criteria which some would consider very conservative[1]. Their criteria for consideration of surgery were met by 43 patients of whom 13 have so far undergone elective operation. Of the 27 patients not undergoing elective operation in whom the outcome is known, aneurysm rupture occurred in two and three died apparently from other causes, a ratio of rupture to incidental death which is to be expected in untreated patients with AAA.

Clinically significant AAAs of $\geqslant$4·0 cm in diameter were detected in 2·4 per cent of men screened but in only 0·35 per cent of women. When resources are limited, screening women for a condition which is seven times more common in men is difficult to justify, particularly when 54 per cent of those attending belong to the sex at low risk of the disease. Approximately 61 patients with AAAs $>$4·0 cm in diameter were detected initially or on follow-up. In the event 70 per cent of these patients met the authors' criteria for consideration of surgery by the end of the study and presumably almost all will eventually. Consideration at the outset of all 61 patients with clinically significant AAAs for elective surgery would have minimized the loss of patients to follow-up, aortic rupture or becoming unfit for surgery.

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1. Collin J. Elective surgery for small abdominal aortic aneurysms. *Lancet* 1987; i: 909.

Authors' reply

Sir

I accept Mr Collin's point that of those patients meeting our strict criteria for considering surgery for abdominal aortic aneurysm (AAA), 30 per cent underwent elective surgery but this amounted to under 10 per cent of all aneurysms detected. This was the conclusion made in our paper and is supported by our data. Some centres operate on aneurysms using less stringent criteria but we feel that if a screening programme is to be effective and not to overload the vascular team, then selective operative criteria are essential. I must emphasize that the two patients whose aneurysms ruptured had been assessed for surgery and one aneurysm ruptured days before a planned operation. The other patient, a woman initially detected as having a 3·2-cm aneurysm which enlarged and ruptured at 5 cm, was deemed unfit for elective repair because of other medical conditions. Ironically, she survived emergency treatment. Our criteria therefore identified all those who were apparently at risk from rupture.

At the time of starting our pilot study in 1984, to our knowledge there were no prospective screening trials under way to examine an unselected population. The mortality rate from this disease for women is lower than that for men but mortality statistics show that the rate increases with age[1] and approximates that for men 10 years later. It therefore seemed worthwhile taking the opportunity to assess prevalence as a function of age in women as well to obtain fundamental information as a basis for decisions on future screening and management.

We are currently analysing a study on 14 000 patients aged 65–80 years of whom half were randomly allocated to a control group and half were offered screening during a 2-year period. Comparisons of incidence of AAA, detection, mortality and operative rates on such a matched population should indicate whether our selection procedures are set at the correct level to prevent rupture without increasing unnecessary surgery.

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Povidone–iodine in experimental peritoneal hydatidosis

Sir

We read with interest the article by Gökçe *et al* (*Br J Surg* 1991; **78**: 495–6) on experimental peritoneal hydatidosis and the effect of povidone–iodine. We disagree with the authors on two points. First, albino rats have forceful host defences against *Echinococcus granulosus*. Heath[1] showed that hydatid cysts did not develop in rats and fibrotic nodules were found on the greater omentum and liver capsule. Dévé[2] and Smyth and Davies[3] found that rats were poor hosts for secondary echinococcosis when protoscolices from sheep were used. Dévé[2] claimed that protoscolices from sheep material could not infect white rats. The differences in host reaction to secondary echinococcosis with different strains of *E. granulosus* could depend on the phylogenetic relationship between the recipient host and donor host antigens previously acquired by the parasite[2–4]. Tezok and co-workers[5] developed secondary hydatid cysts in rabbits and mice, but not in rats, and found that the 25-day-old newly weaned animals were more suitable for secondary hydatidosis than were 5-month-old ones. Sayek and Çakmakçz[4] successfully used mice for secondary hydatidosis in studies concerning mebendazole. Yamashita[6] and Schwabe and associates[7–9] found that immature mice were susceptible to secondary echinococcosis by an intraperitoneal route. Between 1987 and 1991 we have inoculated 200 rats of either sex, aged between 15 days and 14 months, with 1 ml of hydatid scolices suspension (about 1000–10 000 scolices) in the peritoneum and pleura. We have not succeeded in culturing echinococcosis scolices. The same amount of washed scolices were inoculated into 100 mice and echinococcal cysts developed in the peritoneum, but not in the pleura.

Second, it is known that povidone–iodine can kill protoscolices which are outside a brood capsule of *E. granulosus* in either 0·1 or 1 per cent concentration, it is not effective for the protoscolex which is inside a brood capsule. Meymerian *et al.*[10] used povidone–iodine complex in a large series. After the scolex suspension was exposed to the povidone–iodine for 10 min, it was inoculated into the peritoneum of white mice. They concluded the povidone–iodine was of questionable activity.

Scolicidal activity of povidone–iodine is seen within 4–5 min or less because of absorption of free iodine *in vivo*. We believe that the scolicidal activity of povidine–iodine is poor *in vivo* and that rats are not suitable for studies of secondary echinococcosis.

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Authors' reply

Sir

We appreciate the interest of Drs Kolbakır and Erk in our paper. The study presented in our article was preceded by preliminary work to permit familiarization with the various procedures involved and to develop standardized techniques for the preparation of hydatid sand containing an adequate number of viable scolices. The hydatid cysts of sheep were sampled immediately after killing and the methods described in our article were carefully employed to result in a viable scolex count of approximately 15 000/ml, which is higher than that (mean 1000–10000/ml) of the hydatid sand used by Kolbakir and Erk. The occurrence of hydatid cysts correlated positively with the count of viable scolices, rising appreciably at counts above 12 000/ml. We can infer only that the inability of Drs Kolbakır and Erk to observe hydatid cysts in rats compared with mice could have been due to administration of an inadequate number of viable scolices to the former. Sampling sheep cysts at progressively longer time intervals after death leads to corresponding decreases in viable scolex counts. Scolex counts are affected by temperature of the environment and the precipitation time of cyst fluid. Checking the viability of scolices by their motility characteristics ensures a successful inoculation. The rate of successful inoculation increased strikingly after the age of 3 months and at least 3 months was required after inoculation for hydatid cysts to emerge in rats; the use of 3-month-old rats and their killing at the fourth postoperative month in the final study was based on these findings.

We did *not* suggest that povidone–iodine showed scolicidal activity on encapsulated scolices. Our observations indicate that povidone–iodine is highly effective in *preventing* secondary peritoneal hydatidosis. The only other detailed report of the scolicidal activity of povidone–iodine was made by Sungur[1]. In the preliminary stage of our study we found that the results of Sungur were replicable. Drs Kolbakır and Erk are correct that the free iodine in povidone–iodine would be rapidly absorbed by the peritoneum. Their suggestion that this would prevent microbicidal activity is not substantiated by previous studies[2,3]. The total amount of iodine released and not the initial free iodine concentration carries relevance for microbicidal activity. We chose 1 per cent povidone–iodine because it had been used previously in human trials[4], making it possible to extrapolate our results for use in humans and because its free iodine content is only 1 p.p.m.[5]. We have demonstrated that the toxicity of povidone–iodine to liver parenchyma is negligible compared with four other scolicidal solutions, including hypertonic saline[6]. The latter finding constitutes another reason to prefer providone–iodine to hypertonic saline as a scolicidal agent, in view of the frequent hepatic localization of hydatid cysts and their propensity for intrabiliary rupture[7]. Intra-abdominal lavage with povidine–iodine is currently being evaluated for other indications[8] due to its wide spectrum[9] (*Echinococcus granulosus* and other micro-organisms).

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Tension pneumothorax during laparoscopic cholecystectomy

Sir

We were interested to read the Case Report by Whiston *et al.* (*Br J Surg* 1991; **78** 1325) of tension pneumothorax during laparoscopic cholecystectomy. We recently noted a large, right-sided pneumothorax developing at the end of the procedure on a 53-year-old woman Pneumoperitoneum was achieved using carbon dioxide via a variable flow pressure-controlled insufflator In recovery the patient's oxygen saturation (measured by continuous transcutaneous oxygen saturation monitoring) had dropped to 48 per cent. Clinical examination revealed a right-sided pneumothorax, confirmed on chest radiography. While preparations were being made to insert a chest drain, the oxygen saturation was noted to improve and a decision of non-intervention was made One hour later, repeat chest radiography showed the pneumothorax to have completely resolved.

Pneumothorax, as a complication of pneumoperitoneum, was first noted in the 1940s, when pneumoperitoneum was used in the treatment of tuberculosis[1]. Subsequently, there have been many case reports and reviews in the literature of this complication following peritoneoscopy[2–4]. In 1973 Doctor and Hussain[2] promoted the use of carbon dioxide as an insufflating agent because of its high diffusibility.

This carbon dioxide pneumothorax resolved rapidly and suggests that there is a place for conservative management of carbon dioxide pneumothorax

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Identification of bile duct stones in patients undergoing laparoscopic cholecystectomy

Sir

We read the recent paper by Joyce *et al.* (*Br J Surg* 1991; **78**· 1174–6) with great interest. We also perform routine preoperative intravenous cholangiography (IVC) to investigate the biliary tree before laparoscopic cholecystectomy and report similar results.

Between October 1990 and September 1991, we performed elective laparoscopic cholecystectomy on 100 consecutive patients. In ten cases, preoperative endoscopic retrograde cholangiopancreatography (ERCP) was performed because of jaundice (two patients), pancreatitis (two), abnormal liver function tests without clinical jaundice (two) and ultrasonographic evidence of common bile duct (CBD) obstruction (four). Stones were found in only three of the ten and were successfully removed endoscopically after sphincterotomy

The other 90 patients underwent preoperative IVC. One procedure was abandoned due to a vasovagal reaction, and there was a second patient who suffered a mild skin rash In five patients unsuspected CBD stones were demonstrated by IVC and subsequently confirmed and removed by ERCP and sphincterotomy in four patients, with one false-positive result. Of the 85 patients with normal IVCs, one patient required ERCP and sphincterotomy after laparoscopic cholecystectomy to remove a small stone from the lower end of the CBD which caused jaundice Hence, by a combination of preoperative ERCP and IVC, we have prevented retained stones in 7 per cent of patients having laparoscopic cholecystectomy

We have not attempted operative cholangiography in any patient, relying entirely on preoperative IVC to demonstrate anatomy and identify ductal stones. This avoids the difficult decision of how to treat unexpected stones discovered during laparoscopic cholecystectomy. Until the techniques for exploration of the CBD laparoscopically are fully developed, we shall continue to determine the state of the ducts before operation and we entirely agree with the authors that IVC is a safe and effective method of doing this.

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Book reviews

Interventional Computed Tomography

R. M. M. Seibel, D. H. W. Gronemeyer, eds. 292 × 215 mm. Pp. 355. Illustrated 1990. Blackwell. £95

Do you want a book that will tell you everything you want to know about interventional computed tomography (CT) and considerably more besides? If so, then this is the book for you – at a price.

Interventional radiology is one of the fastest growing subspecialties in medicine, and the imaging potential of CT makes it the best technique for many procedures. This book is a comprehensive text on interventional CT and is written primarily for the radiologist as a reference work. It gives detailed instructions on technique and is lavishly illustrated with both CT images and anatomical specimens to illustrate the gross anatomy. It is a large, multiauthor book written by some acknowledged experts in the field, the bulk of the authors being German.

The first section of the book deals with CT guided biopsy which is the indication for which most surgeons are familiar and indeed grateful. The list of sites for which the technique of biopsy is described is impressive, and includes the head, neck, thorax, abdomen, pelvis and skeleton The second section deals with therapeutic procedures and the majority of these relate to interventions on the vertebral column and nervous system, including the treatment of pain resulting from malignant disease. Most of these techniques require an imaging system such as CT or magnetic resonance imaging. The next section covers the drainage of intra-abdominal abscesses and biliary and urinary tract interventional procedures. These last two indications are presumably included for completeness, since CT is a most inconvenient technique for imaging in these situations.

In short, this is an exhaustive, lavish and expensive book on one aspect of interventional radiology. It is one for the radiology department library and not for the surgeons' personal collection.

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Surgical Management. 2nd ed.

N. J. O'Higgins, G. D. Chisholm and R. C. N. Williamson, eds. 276 × 206 mm Pp. 1007. Illustrated. 1991. Oxford· Butterworth–Heinemann. £49·50.

Writing a comprehensive textbook has always been difficult and is getting more and more so. The range of subject matter grows all the time, knowledge and practice change more quickly than in conventional publications, and contributors and editors are ever more busy. In consequence the advice tended a quarter of a century ago is still sound, but is still disregarded for a number of reasons[1] There is apparently a demand and money to be made, there is the compelling urge of authors and editors which is almost a disease, though of course a productive one One sign of this is that *Surgical Management* requires a second edition 8 years after its successful launch.

The editors hope that the book will give guidance to those sitting higher examinations and also be a companion to the practising surgeon. As to the first, assessment, in the UK at least, is undergoing change though the implications of this for the curriculum are sometimes hard to assess. The early chapters of the book on principles address effectively most of the knowledge necessary for the scientific basis of the practice of surgery and are as up to date as is possible given the problems to which I have already referred As to the second, I am a little less confident because the confines of size have inevitably reduced the amount of detail and straightforward practical advice that can be conveyed. I could, for example, find little on the precise diagnosis and management of supramalleolar ulcer of varicose origin; this was not mentioned at all under varicose veins and referred to only in passing in the section on plastic surgery. Although human immunodeficiency virus infection is mentioned a number of times, the question of what policies to adopt with the seropositive patient and the influence of the virus on surgical disease, particularly in sub-Saharan Africa, is not considered. Closer to home, the symptoms that might be ascribed to piles are poorly discussed and though lateral sphincterotomy for fissure is mentioned the operation is not described nor is its possible effect on continence considered. The problems of effective editorship are illustrated by the fact that adult respiratory distress syndrome is described twice in nearly identical terms without any cross-reference. Inevitably, laparoscopy gets only minor consideration in two areas where it is now a strong performer – minimally invasive surgery and diagnosis in the acute abdomen.

However, such obsolescence is what the quoted paper referred to as an unfair target for the snide reviewer. This text is a worthy one, well produced and with, for the most part, good and relevant illustrations, though I do not think that the picture of a well known and expert professor contemplating the control panel of a lithotriptor contributes a great deal to surgical education. It will certainly steer the surgical trainee in what is perceived as the right direction, though his or her knowledge will require considerable supplementary feeding from other sources.

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1. Dudley HAF. Textbooks: a time to stop. *Lancet* 1966; **i**: 589–90.

The Crimean Doctors – A History of the British Medical Services in the Crimea War. Vols 1 and 2

J. Shepherd 216 × 140 mm. Pp. 344 + 673 1991. Illustrated Liverpool Liverpool University Press. £32.

Most readers of this Review will know the Crimean War only as the background to the charge of the light brigade and for the work carried out by Florence Nightingale in the Barrack Hospital at Scutari In fact it deserves to be more widely remembered: for the military strategic lessons that were learnt and successfully implemented in later wars; for the medical and surgical lessons that were learnt and then forgotten in later wars; for the effect it had on improving the lot of the non-commissioned soldier; and for being the stimulus to much-needed improvements in organization and education in the army medical services. It was a relatively short war, less than 1 year of fighting, and its history can therefore be readily assimilated.

Although there exists a considerable literature on the military aspects of the campaign and a veritable torrent of writing about Miss Nightingale and her work, there has been remarkably little published about the medical and surgical aspects of the conflict other than contemporary accounts now very difficult to obtain. John Shepherd, well known for his lucid and authoritative writings on abdominal surgery, has turned his attention in retirement to rectifying this gap in medical history and has written a scholarly and absorbing study which is leavened by a judicious choice of illustrations. Over a decade or more he consulted every known printed primary source as well as much manuscript material and succeeded in collating this mass of data into a logical sequence with the prime aim of describing the campaign as recorded by the doctors who took part

Volume 1 broadly covers the evolution of the army and naval medical services up to 1854, the early battles, the devastating effects on the British army of illness, especially dysentery and cholera, and the arrival of Florence Nightingale at Scutari Volume 2 covers the conditions at Scutari, the long drawn-out siege of Sebastopol, the civil hospitals and surgeons, the role of the navy medical services and the after-effects of the war Each chapter is extensively referenced and most contain verbatim extracts from letters and diaries written by participants; these give an immediacy which enhances the descriptive passages. There are many statistics relating to numbers of admissions, injuries, deaths, illness and so on at various times of the campaign, but these are in small print and can be omitted by the general reader. Biographical details are given of the doctors who served in the war, of whom the best known today is Spencer Wells. Surprisingly, no doctor was killed in action or seriously wounded although several died from disease. Three doctors were awarded the Victoria Cross for outstanding bravery on the field of battle.

This outstanding contribution to military and medical history will be a major reference source, necessary on the shelves of all medical libraries. It is also warmly recommended for the personal libraries of readers of this Review, all of whom have an indirect link with the Crimean War. On 8 September 1855, Sergeant Andrew Moynihan, aged 24, killed five enemy troops and rescued two fallen British while receiving 12 wounds himself For this feat he was awarded the Victoria Cross Had he been killed in this action the founder of *The British Journal of Surgery*, his son Berkeley Moynihan, would never have been born

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Leg Ulcers – a Practical Approach to Management

D Negus 240 × 167 mm. Pp 181 + x Illustrated 1991. Oxford· Butterworth–Heinemann £35

This book is a very practical and up-to-date monograph, encompassing the pathophysiology, investigation and treatment of venous ulceration

For a condition which affects over 100 000 people in the UK at any one time, with a further 1 000 000 potential ulcer sufferers, the condition is poorly understood, and very poorly treated. A full and comprehensive historical review of leg ulceration and the importance of differentiating ischaemic ulceration is undertaken. Anatomical abnormalities are well recognized and described. The chapters on calf muscle pump function and pathophysiology describe in detail the hypotheses thought to underlie venous ulceration. These chapters alone provide an up-to-date source of information. This is an extremely well referenced monograph

Part 2 of this book, on Practical Applications, clearly reflects the Author's preference with regard to investigation and treatment A comprehensive section on methods of diagnosis, including both non-invasive techniques, venography and arteriography is well written Emphasis is placed on the importance of making a diagnosis, and the differential diagnosis of other types of leg ulcer A significant portion of this book is related to the differential diagnosis There are some extremely good illustrations, it is a pity that they are all black and white. The book is completed by discussion on pharmacological agents, the management of recurrent venous ulceration, and surgical and sclerotherapy treatment of varicose veins

This book contains an enormous amount of information. It is extremely well referenced, and would provide a very useful starting point for a surgeon interested in the management of patients with venous ulceration Whilst the book clearly reflects one man's considerable experience over a number of years, David Negus has gone to a lot of trouble to ensure that this book is up to date.

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Atlas of Hernia Surgery

G E Wantz 285 × 220 mm. Pp 240 Illustrated. 1991. New York Raven Press. $144.

That this atlas should be necessary in 1991 is a reflection on the way hernia surgery is taught to surgical trainees. George Wantz has become a hernia specialist after training in vascular surgery, and his referral practice has shown him how many technical errors are still made for correction at later operations The surgical techniques illustrated are those he has tested personally, and Caspar Henselmann's drawings are delightfully clear in a way that operative photography can never be.

I suspect that all surgeons in training and many consultants could benefit from a close study of this book. I believe that if the drawings on pages 62 and 63 of 'Corrupt Bassini repair' and 'Authentic Bassini repair' were fully understood and put on the noticeboard in all surgeons' rooms in this country, the recurrence rate for inguinal hernia repair would fall dramatically The choice of surgical techniques for repair is left open to the reader Wantz prefers the Shouldice technique for primary hernias and Stoppa's reinforcement with Mersilene mesh (Ethicon, Edinburgh, UK) for difficult, bilateral or recurrent hernias Their mutual experience of this technique will probably lead to its wider use and acceptance in the future.

My only real criticism of this book is the lack of any recurrence rates to give surgical trainees and their peers guidance. The McVay technique has proved unsuccessful in several European series, while the Shouldice technique gains more advocates with time. Dr Wantz tells me that the transposition of E and F in the text on page 9 is one of several errors! I did not find any others and strongly recommend this excellent atlas to a wide audience.

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Wylie's Atlas of Vascular Surgery: Complications Requiring Reoperation

R J Stoney and D J. Effeney 286 × 221 mm. Pp. 194 Illustrated 1991. Philadelphia: J B Lippincott £150.

Complications Requiring Reoperation is one of a collection of six volumes, collectively called *Wylie's Atlas of Vascular Surgery*, which are designed to present current strategies of vascular surgical management. The present volume deals with the serious complications of reoperation of the aorta and the carotid, visceral, renal, iliac and infrainguinal arteries.

It is correctly called an atlas as almost every page has one or more illustrations, usually in colour. These are mainly artwork, although some are clinical photographs. Although these good quality illustrations help us to understand the rather sparse text, there is a tendency to illustrate rather simple concepts which will already be well known to those dedicated vascular surgeons who will choose to read the book.

It is a friendly looking volume with uncrowded text and takes about 4 h to read from cover to cover. It is burdened by neither references nor bibliography, but the many *ex cathedra* statements are probably acceptable and, in any event, coming as they do from authors of such distinction, are worthy of our consideration. This book describes an accumulated experience derived over 40 years of vascular surgical complications at the University of California, San Francisco As such, it is for those surgeons whose practice contains a large element of arterial operations.

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Atlas of Breast Disease

V Barth and K. Prechtel 304 × 215 mm Pp 262 + ix. Illustrated 1991. Philadelphia B. C Decker £88

This handsomely illustrated volume is written by a radiologist and a pathologist and its basic purpose is to give correlating pictures of mammograms, macroscopic pathology and histology. Some ultrasonography scans are also included. The quality of the macroscopic illustrations is high but the quality of the mammograms and of the histological pictures is variable. A surgeon might well find a library copy useful for the radiological and macroscopic pictures, but the text is unlikely to be attractive to surgeons, or probably to UK doctors in general. Although the book was translated from the original German in America, the quality of the translation is often indifferent and there is a fair amount of unusual terminology For instance, 'polycyclical' is a favourite word and the term 'mastion' is used frequently; it seems to refer to a lobuloductal unit There are obtrusive printing errors which grate on the reader.

The chapter on indications and results of different examination techniques is confusing As an example, pneumocystography is recommended before mammography in all cases where a cyst is suspected on clinical grounds. Yet the same section states that pneumocystography is not indicated when the mammogram or ultrasonogram shows no irregularity It is not clear whether these inconsistencies arose during translation, but they limit the book's use as a textbook of breast investigation.

In summary, this is best regarded as an atlas with fine pictures of macroscopic breast disease and radiological correlates covering a very wide range of breast conditions.

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Surgery for Endocrinological Diseases and Malformations in Childhood

P. P. Rickham, T A. Angerpointner, M. W. L. Gauderer, W. Ch. Hecker, J. Prevot, L. Spitz and U. G. Stauffer 234 × 156 mm. Pp. 144 + x. Illustrated. 1991 Germany Springer-Verlag

This is a slim volume of 136 pages excluding the index. It contains a few interesting papers from North America, especially those concerning parathyroid surgery by A. J. Ross of Philadelphia, phaeochromocytoma (persistently spelt 'pheochromocytoma') by E. W. Fonkalsrud of Los Angeles and an unexpected chapter on neuroblastoma by M. L. Nieder and M W. L Gauderer of Cleveland.

There are no contributions from the UK or Australasia. The bulk of the text consists of disappointingly feeble contributions from central and eastern Europe, some amounting to little more than case reports. There is little new or exciting in these pages. One can only wonder why iodized table salt is not taken invariably in the goitrogenic regions of central Europe, where 10 per cent of adolescents (rising to 84 per cent in South Tyrol) still present with iodine-deficient goitre (pages 16 and 22). That this is so suggests that there are poor standards of health education in those areas, in which case the authors should be doing something to correct the situation.

Several of the papers were obviously written in the contributors' native tongue and then poorly translated into an irritating pseudo-American jargon vaguely resembling English, e g 'strumectomy', 'anamnestically' and 'surgical radicality'. The illustrations are simple and clearly reproduced and the print is easy to read despite several spelling mistakes The printers have performed their task well, but the book is lacking in academic content, possibly because surgery is so infrequently required for diseases of the endocrine glands of children. Perhaps there is nothing new to be written on this subject. certainly the book contains very little that is novel

Apart from the contributions from North America this book is hardly worth reading and I would not buy it.

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Principles and Practice of Research: Strategies for Surgical Investigators. 2nd ed.

H. Troidl, W. O. Spitzer, D. S. Mulder, A S. Wechsler, B. McPeek, M. F. McKneally and C. M Balch, eds. 260 × 184 mm Pp. 566 + xxviii. Illustrated 1991. New York Springer-Verlag. £70 50

The maintained pressure on junior surgeons to undertake a research project is re-emphasized by the recent appearance of a new edition of *Principles and Practice of Research· Strategies for Surgical Investigators* This second edition reflects the feedback obtained from readers of the first edition published in 1986, and is 50 per cent larger in size (and cost) The editors have set out to provide in a single volume 'a proper framework for the organization of surgical research'. It is therefore intended equally for both the newcomer and the experienced researcher. As such, it is probably too cluttered for the former and certainly too exhaustive (and exhausting) for the latter. Much of the content is confirmatory and repetitive rather than vitally illuminating, especially for the latter group of readers

Its range is, however, extensive and impressive. On average approximately 12 chapters each are devoted to: (1) the background to and a historical perspective of surgical research and researchers, (2) getting a research project successfully off the ground, including how to perform statistical analysis of the acquired data; (3) the methodology of research, including a curiously isolated piece on recombinant DNA technology, (4) the best means of approaching the communication of one's research data to the scientific community at large, including the extraordinary inclusion of a short essay on coping with jet-lag. The volume is concluded by reports of surgical research from 12 countries, evidently an attempt to balance the strong North American flavour of the rest of the book.

This book does have many valuable attributes the emphasis throughout of constantly applying research to the *clinical* environment and the pivotal role of the Professor or Chairman of Surgery in establishing a flourishing research-based unit; good advice on how to tame the literature explosion, the importance of sample size in clinical trials; the recognition of research endpoints; an excellent description of the precision criteria of diagnostic tests; a sensitive chapter on animal experimentation; and helpful, if repetitive, comments on the presentation and publication of data.

Anyone involved with surgical research should make time to read this book. Its commitment to improving surgical research on a global scale is sobering and yet at the same time stimulating Its readers cannot fail to be inspired to raise their research aspirations, though they must be prepared to sift through a large volume of text to reach this exalted position

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Head and Neck Oncology for the General Surgeon

P. E. Preece, P D. Rosin and A G D. Maran 235 × 158 mm. Pp. 256 + viii. Illustrated 1991. London: W B. Saunders. £37.

This little black book, which is a compilation of the contributions of 24 authors to the 1988 BASO Forum on Head and Neck Oncology, achieves its stated aim of informing the generalist without being overdetailed

It opens with reviews of the epidemiology, histopathology and the multidisciplinary management of thyroid neoplasms. There is a useful review of multiple endocrine neoplasia syndromes and their relationship to the thyroid and parathyroid glands. The lion's share of the book is given to salivary tumours. There is a comprehensive and instructive section on the preoperative assessment of, and primary surgery for, parotid tumours, including an account of the Middlesex Hospital experience over the 20 years to 1988. The management of recurrent pleomorphic adenomas, facial nerve reconstruction and the place of radiotherapy and chemotherapy each have their own chapter. Other malignant lumps in the neck are considered in a short but concentrated final chapter

Such a book is inevitably prone to repetition and minor inconsistencies, but it is well formatted and referenced, with clear and appropriate black-and-white illustrations. It gives a lucid and concise account of the management of head and neck tumours, and will be of value to the trainee as well as to the general surgeon seeking to keep up to date in this area.

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Atlas of Orthopaedic Surgical Approaches

C. L. Colton and A. J. Hall 286 × 225 mm. Pp 216 + viii. Illustrated 1991 Oxford· Butterworth–Heinemann £80.

This handsome, 200-page, hardback book has been written by a small group of distinguished surgeons in the UK and North America, and is aimed at surgical trainees and their tutors.

It is an excellent text on the topic, each chapter covering a specific area of the body and outlining the many surgical approaches. I particularly like the logical way in which the chapters are laid out, with discussions of relevant anatomy that are excellent, and detailed descriptions of the positioning of the patient, access, incision, approach and indications following in sequence.

The general format makes this book easy to read It has a bold style and clear headings, the text and line illustrations, which are all to a high standard, correspond Indeed, my only real criticism of the book is that there are two or three chapters, dealing particularly with the elbow and forearm, where the illustrations are on a separate page from the text, making it difficult to follow the approach Otherwise, this is an excellent and elegantly produced textbook, which I would certainly recommend to all surgeons as a comprehensive and clear description of orthopaedic surgical approaches.

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Notices and announcements

5 May 1992
Surgery in the Developing World – The Challenge to Britain
London, UK
Information. Keith Newton, Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, UK

9 May 1992
Methods and Procedures of Medical Ethical Committees Within the EC
Limburg, The Netherlands
Information: Annie Simon, Faculty of Health Sciences, University of Limburg, PO Box 616, 6200 MD Maastricht, The Netherlands

10–16 May 1992
Acute Trauma Management
Belfast, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

14–15 May 1992
British Association of Endocrine Surgeons Meeting
Canterbury, UK
Information: Mr A. W. Goode, The Surgical Unit, The Royal London Hospital, London E1 1BB, UK

15 May 1992
Abdominal Aortic Aneurysms – Assessment and Management
Ayr, UK
Information: Mr G. Stewart, The Ayr Hospital, Dallmington Road, Ayr KA6 6DX, UK

17–23 May 1992
Recent Advances in Endocrinology and Metabolism
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

20–23 May 1992
83rd Meeting of the American Association for Cancer Research
San Diego, California, USA
Information: American Association for Cancer Research, Inc., Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, PA 19106-3483, USA

27–29 May 1992
European Council for Coloproctology Fourth Biennial Congress
Marseille, France
Information: Patricia Vallet, Alice Congrés, 12 Cours Jean Ballard, BP 2028 13201 Marseille cedex 01, France

2–5 June 1992
Eurochirurgie '92 2nd European Congress of Surgery
Brussels, Belgium
Information. Congress Secretariat: Eurosurgery '92, Brussels International Trade Fair, Place de Belgique, B-1020 Brussels, Belgium

3 June 1992
Surgical Problems in Early Breast Cancer
Solihull, UK
Information: Mrs V. Hall, British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

5 June 1992
Logistic Regression and Survival Analysis
Limburg, The Netherlands
Information: Annie Simon, Faculty of Health Sciences, University of Limburg, PO Box 616, 6200 MD Maastricht, The Netherlands

7–10 June 1992
International Congress on Cancer of the Esophagus
Genoa, Italy
Information: Secretariat, Luigina Bonelli, Unit of Clinical Epidemiology and Trials, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

7–11 June 1992
4th World Congress of Hepato-Pancreato-Biliary Surgery
Hong Kong
Information: Secretariat, International Conference Consultants Ltd., Suits A and B, 16/F., Casey Building, 38 Lok Ku Rd, Sheung Wan, Hong Kong

24–27 June 1992
The Endocrine Society 74th Annual Meeting
San Antonio, Texas, USA
Information: Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

28 June–3 July 1992
4th Oxbridge Organ Transplantation Course
Cambridge, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

29 June–3 July 1992
Practical Nutritional Support – Third Annual Training Course for Clinicians
Southampton, UK
Information: Mr Brendan Moran, Department of Human Nutrition, University of Southampton, Southampton SO9 3TU, UK

2–3 July 1992
Surgical Research Society Meeting
Edinburgh, UK
Information: Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

5–10 July 1992
Immunology and the Nervous System: Clinical Aspects
Oxford, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

10–11 July 1992
Hong Kong Surgical Forum – Summer 1992
Hong Kong
Information: Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

10–12 July 1992
Minimally Invasive Medicine – From Diagnosis to Therapy
Berlin, Germany
Information: KIT Marketing Services GmbH, Behrenstraße 23, 0-1080 Berlin-Mitte, Germany

13–17 July 1992
Annual Diagnostic Imaging Seminar
Martha's Vineyard Island, Massachusetts, USA
Information: Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, USA

16–18 July 1992
XVIIth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, University Department of Medicine, Royal Free Hospital, London NW3 2QG, UK

22–24 July 1992
British Association of Paediatric Surgeons XXXIX Annual International Congress
Leeds, UK
Information: Secretariat (BAPS), Bell Howe Conferences, 1 Willoughby Street, Beeston, Nottingham NG9 2LT, UK

2–4 September 1992
Ultrasound Angiography '92
Southampton, UK
Information: Secretariat, Ultrasound Angiography '92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK

9–11 September 1992
2nd Nottingham International Breast Cancer Meeting
Nottingham, UK
Information: Mrs Wendy Bartlam, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

20–23 September 1992
VIIth Edmondo Malan International Day of Surgery – Endo-Laparoscopic and Mini-Invasive Surgery
Parma, Italy
Information: Professor Gian Carlo Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43100 Parma, Italy

24–26 September 1992
Postgraduate Course – Principles of Colon and Rectal Surgery
Minnesota, Minneapolis, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue Southeast, Minneapolis, Minnesota 55414, USA

SURGERY

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Year Book
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Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title page should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies of original articles and other editorial matter to. The Senior Editor, The British Journal of Surgery, Butterworth–Heinemann Ltd, 59/60 Grosvenor Street, London W1X 9DA, UK. Telephone: 071-493 5841. Facsimile: 071-499 3384.
Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

Rejected manuscripts will not be returned to the authors, unless this is specifically requested.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs which might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission signed leading articles to *The British Journal of Surgery* These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

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The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 500 words, with no more than five references and one illustration

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These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

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The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

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The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications.* New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

EUROSURGERY

Promoting Research and Training in Surgery

European Congress of Surgery

2–5 June 1992
Brussels

The Second European Congress of Surgery 'Eurosurgery 92' will take place in Brussels in June 1992. This meeting will pursue the aims of Eurochirurgie/Eurosurgery to promote research and training in surgery.

Preliminary Scientific Programme

I. General topics

2 June	What is new in European surgery? Computers in clinical surgery AIDS and surgery New aspects of laser surgery
3 June	Surgery in the aged
4 June	War/tropical surgery Ambulatory surgery History of surgery
5 June	Decision making in surgery Theoretical surgery Insurance implications in surgery Stapling in surgery Cost of surgical activity Organization of the operative complex Surgical nursing symposium

II. Abdominal and Oncological Surgery

2 June	Gastro-oesophageal reflux Gastric stump cancer Colon cancer Hydatid cyst of the liver Motility disorders of oesophagus
3 June	Saving the spleen Diverticulitis of the colon Colonic volvulus Laparoscopic cholecystectomy symposium Prospects and future of laparoscopic surgery Colon carcinogenesis
4 June	Abdominal surgery by laparoscopy Laparoscopic surgery: training Cancer of the oesophagus Oesophageal diseases Reducing sepsis in colorectal surgery Infections in abdominal surgery Liver metastases Hirschsprung's disease Major hepatic surgery
5 June	Acute pancreatitis Radical surgery in rectal cancer Adjuvant treatment in rectal cancer Stoma therapy Stapling in surgery

III. Training in Surgery

2 June	Specialisation in general surgery
3 June	Training in surgery Surgical training in Eastern Europe
4 June	Laparoscopic surgical training Surgical video session

IV. Transplantation Surgery

5 June	Multiorgan harvesting and preservation in Europe Transplantation in Belgium Immunosuppression regimens Liver transplantation: new prospects

V. Traumatology and Orthopaedic Surgery

3 June	Saving the spleen
4 June	Early management of multiple trauma Arthroscopic surgery in 1992 Hand surgery Treatment of major pelvic trauma

VI. Paediatric Surgery

4 June	Hirschsprung's disease

VII. Thoracic and Oncological Surgery

2 June	Early breast cancer Gastro-oesophageal reflux Oesophageal motility disorders
3 June	Advanced breast cancer
4 June	Lung metastases Oesophageal diseases Cancer of the oesophagus
5 June	Stapling in surgery

VIII. Endocrine Surgery

3 June	Satellite disorders of hyperthyroidism
5 June	Diagnosis and multimodal therapy of thyroid cancer

IX. Vascular Surgery

5 June	Endovascular surgical procedures Abdominal aortic aneurysm Prostheses in vascular surgery

X. Plastic Surgery

4 June	Burn injury Microsurgery Hand surgery Malignant tumours of the face

XI. Gynaecological Surgery

3 June	Gynaecological laparoscopy

Abstracts of the free papers will be published as a supplement to The British Journal of Surgery.

For registration forms and further details contact:

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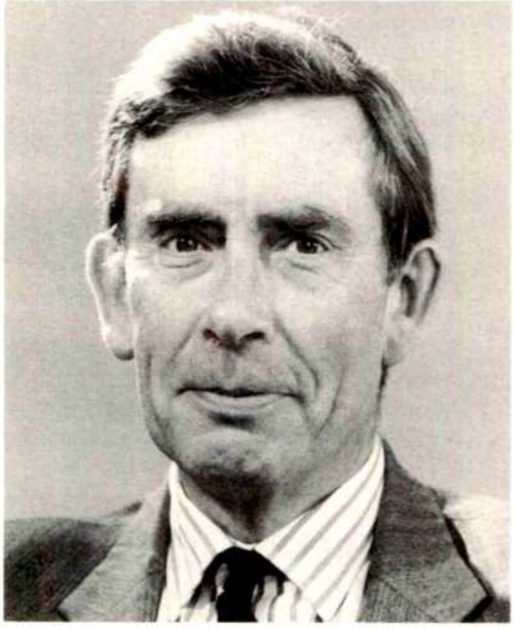
Officers of The British Journal of Surgery Society

The organization and the hierarchy of The British Journal of Surgery *are a little complex. The Journal is owned by* The British Journal of Surgery Society *on behalf of the surgeons of Great Britain and Ireland. It is administered by the* Council *of that Society; the Articles of Association limit the Members of Council to 15 in number. There are three representatives of the Editorial Team on Council and three privileged Members, who are appointed by the Royal Colleges of Surgeons, the Association of Surgeons of Great Britain and Ireland, and the Surgical Research Society. The* Editorial Committee *is responsible for the day-to-day running of the Journal. It comprises the 15 Members of Council, the full Editorial Team, co-opted Members (including, at present, three European surgeons) and representatives of the publishers. The Editorial Committee is supported by a much larger* Editorial Board *(some 80–90 strong), which includes surgeons from the British Isles, Europe and the rest of the World; 38 countries are represented at the present time. By custom, the British Isles Members of the Editorial Board constitute the Members of The British Journal of Surgery Society, and they elect the Council and Officers of the Society at the Annual General Meeting.*

Since readers might wish to know who is responsible for The British Journal of Surgery, *we intend to introduce the Members of the Editorial Board issue by issue, starting this month with the Chairman and the two Vice-Chairmen.*

Chairman

MR CRAWFORD JAMIESON



Crawford William Jamieson was born in 1937 and qualified as a doctor from Guy's Hospital in 1960. Like many of his generation he obtained the conjoint qualification of the Royal Colleges (MRCS, LRCP) as a precaution against the unlikely event of failing the university degree (MB, BS). After early training in the home counties of England and on board ship, he became a surgical registrar at Cambridge and then at St Mary's Hospital, London. In 1968 he went to Tulane University, New Orleans as Wellcome Research Fellow. Nineteen seventy was Crawford's annus mirabilis: in that year he obtained a consultant appointment at St Mary's Hospital, the Mastership of Surgery degree (University of London) and a Hunterian Professorship at the Royal College of Surgeons of England. Two years later he was appointed to the staff both at the Hammersmith Hospital and at St Thomas' Hospital, London, where he now undertakes most of his work. Mr Jamieson's publications reflect his detailed interest in several different aspects of vascular surgery, both arterial and venous. He has been Secretary and Treasurer of the Vascular Surgical Society of Great Britain and Ireland. His association with *The British Journal of Surgery* began with Assistant Editorship in 1977. The following year he took over as Editor from Mr Felix Eastcott, serving until 1987. He was elected Chairman of the BJS Society in 1988. Perhaps nine years' service as Editor of the Journal accounts for the faintly quizzical expression to his features.

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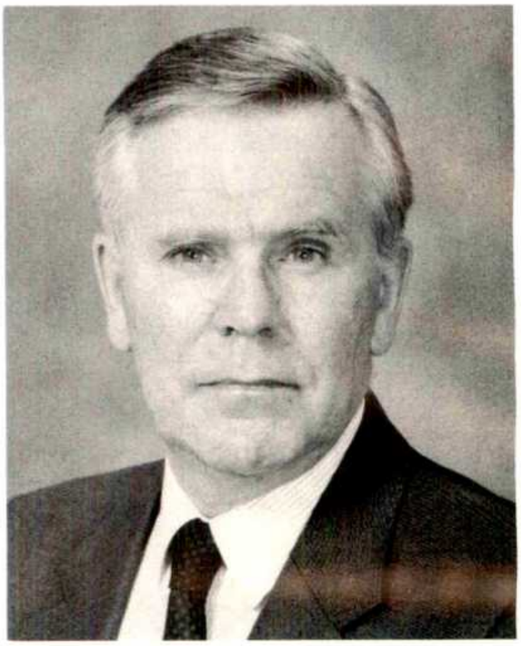
Vice-Chairman

MR BRENDAN DEVLIN

Hugh Brendan Devlin was born in Lancashire in 1932 and educated at Trinity College Dublin, where he qualified in 1957 and where he later obtained two higher degrees (MD 1963, MCh 1966). After training in Dublin, Liverpool and London he became a consultant surgeon at North Tees General Hospital and Lecturer in Clinical Surgery to the University of Newcastle upon Tyne. He is a Fellow of the Surgical Colleges in England, Scotland, Ireland and the USA. In 1970 he was Arris and Gale Lecturer at the Royal College of Surgeons of England, and he has given other named lectures to the Irish College, the Royal College of General Practitioners, and the Association of Surgeons in India and Poland. Brendan Devlin is a past President of the Surgical Section of the Royal Society of Medicine. He has served on the Council of the Association of Surgeons and is a current Member of Council of the Royal College of Surgeons of England, where he is also Chairman of the Clinical Audit and Quality Assurance Committee. He is well known throughout the UK for his work as clinical coordinator to the Confidential Enquiry into Perioperative Deaths. His catholic interests in surgery embrace abdominal hernias (subject of a recent book), stoma care, peptic ulcer disease and many different aspects of surgical audit. His long and charismatic association with the BJS Society began in 1978, and he has been Vice-Chairman since 1981. To Brendan in particular we owe the present cover of the Journal.

Vice-Chairman

PROFESSOR SIR ROBERT SHIELDS



Robert Shields was born in 1930 and qualified from Glasgow University in 1953. He obtained his Edinburgh Fellowship in 1959 and his English Fellowship in 1966. For his MD thesis on the intestinal absorption of fluid and electrolytes he obtained the Bellahouston Gold Medal of the University of Glasgow in 1965. Following national service in the Army, he trained at the Western Infirmary, Glasgow, the Mayo Clinic and the Welsh National School of Medicine before being appointed to the Chair of Surgery at the University of Liverpool. Between 1982 and 1985 he served as Dean to the Faculty of Medicine at Liverpool. His main clinical interest has been in portal hypertension. His lustrous career contains appointments and distinctions that are too numerous to name but have included: Membership of the Council of the Royal College of Surgeons of Edinburgh, the General Medical Council, the Hunterian Institute and Court of Examiners (English College) and the Medical Research Council; President of the Association of Surgeons, the British Society of Gastroenterology and the Surgical Research Society; and Honorary Fellowship of the American and South African Colleges of Surgeons. He is an Honorary Doctor of Science in the University of Wales. He was knighted in 1990 and commissioned Deputy Lord Lieutenant of Merseyside in 1991. He was appointed Vice-Chairman of The British Journal of Surgery Society in 1989.

Robin Williamson

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Impotence

The discovery by Virag[1] in 1982 that the intracorporeal injection of papaverine could produce an erection, and the pioneering work of Brindley[2] in 1983 have led to the development of successful self-injection programmes using a variety of vasoactive agents; these have revolutionized the management of impotence. Published reports[3] indicate that more than 3000 patients have been given papaverine, almost 4000 the combination of papaverine and phentolamine, and 1284 prostaglandin E_1.

Formerly it was considered important to differentiate psychogenic from organic impotence using nocturnal penile tumescence studies, but the most relevant contemporary screening test is whether or not the impotent patient responds to intracorporeal papaverine. Almost all patients with psychogenic erectile failure or impotence owing to neurological causes will respond. Even if history and clinical examination suggest the likely cause to be vasculogenic, it is still worth trying intracorporeal papaverine; patients who do not respond can be offered a choice between a vacuum constriction device and a surgically implanted penile prosthesis.

There is, however, increasing interest in penile revascularization procedures and 'venous leak' surgery, both of which require further investigation to select those patients who are likely to benefit. Standard duplex ultrasonography[4] to evaluate cavernosal arterial blood flow has been superseded by colour-coded duplex scanning[5], which more readily locates the cavernosal arteries in the flaccid state and allows better determination of the angle of incidence of the Doppler beam. If the patient has impaired vascular inflow and is a suitable candidate for corrective vascular surgery (e.g. those with congenital or traumatic arteriovenous fistulae, or younger patients with post-traumatic local vascular injury, rather than vasculopaths or diabetics[6]), selective pudendal arteriography should be the next step. This investigation must be performed after intracorporeal papaverine injection and is enhanced by digital subtraction[7]. If there is demonstrable occlusion of the cavernosal arteries, various surgical options are available. Currently the most popular techniques use optical magnification to aid anastomosis of the mobilized inferior epigastric artery either to the deep dorsal vein of the penis, which is ligated proximally and distally (Virag procedure)[8], or end-to-side to a dorsal penile artery with side-to-side anastomosis of the latter to the deep dorsal vein[9]. A plea, however, for better patient selection, assessment of operative outcome and reporting of results is well founded[10].

If a patient fails to respond to intracorporeal papaverine but has normal penile arterial inflow, dynamic cavernosometry or cavernosography needs to be undertaken to detect and assess venous leak or 'failure to store' impotence[11,12]. The results of surgery directed at reducing the venous outflow from the penis, mainly by deep dorsal vein ligation and stripping, together with stripping of the circumflex veins and sometimes the crural veins, or crural ligation or plication, are less impressive with longer follow-up. The veno-occlusive mechanism of the human penis is complex and it is simplistic to believe that the problem lies with the extracorporeal venous drainage system. Evidence is accumulating that the defect lies within the tunica albuginea in the erectile tissue of the corpora cavernosa itself, i.e. end organ failure.

In conclusion, with the development of successful self-injection programmes, it is now possible to provide practical help for the majority of men with erectile dysfunction. The older vasculopath or diabetic who does not respond can be offered a vacuum constriction device after suitable instruction. If a penile prosthesis is chosen, it is important that a detailed discussion with the patient and his sexual partner is undertaken before operation. The more refined and sophisticated investigations of

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colour-coded duplex scanning, digital subtraction selective pudendal arteriography, and dynamic pharmacocavernosometry can be reserved for patients likely to benefit from penile revascularization or venous leak surgery. Perhaps this should be within the specialized remit of the uroandrologist in the 1990s.

J. C. Gingell

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Autotransfusion with salvaged blood

> 'I advocate it as perfectly sane and capable of saving many lives in the major operations of surgery ... to my own mind the principle of reinfusing the patient [with blood] is now definitely established.'
>
> (Duncan J. *Br Med J* 1886; i: 192)

Dr John Duncan would be bemused to see surgical transfusion practice now, more than 100 years after he successfully reinfused blood shed during an above-knee amputation. Instead of pursuing the logical principle of conservation through recycling, surgeons rely almost entirely on third party donor blood.

Intraoperative autotransfusion (IAT) is the salvage and reinfusion of blood shed during surgery. Modern techniques developed during the Vietnam and Korean wars have been refined, culminating in sophisticated centrifugal cell-saving equipment. A second method in current use collects shed blood into a reservoir consisting of a collapsible plastic bag within a rigid shell for reinfusion without washing. The systemic heparin used in cardiac and vascular surgery prevents clotting during collection. Cell savers, however, anticoagulate shed blood at the sucker tip and can thus be used in patients who have not received heparin. Concerns about the safety of IAT have now been largely overcome. Air embolism, haemolysis and the reinfusion of microparticulate debris are now of only historical interest. The single reported case of air embolism associated with the use of a cell saver occurred because of incorrect operation; the method has an enviable safety record.

Blood processed in a cell saver has a haematocrit of 0·55–0·65. Red cell survival and 2,3-diphosphoglycerate levels are normal. Younger erythrocytes are more likely to survive the salvage process; older cells undergo lysis. Recent research has examined coagulopathy after IAT. Reinfusion of blood which has been 'activated' by an air interface, plastic components, tissue juice and other thromboplastic stimuli may theoretically precipitate disseminated intravascular coagulation. Fibrin degradation products are markedly increased in shed blood and are not completely removed by washing. Demonstration of the antigen D dimer implies that blood has clotted and subsequently undergone fibrinolysis, but D dimer does not persist after IAT, and disseminated intravascular coagulation has not occurred using modern equipment. Circulating inhibitors probably buffer infused activated clotting factors and fibrinolytic products, but experimental confirmation of this is difficult because of background haemostatic changes that occur during surgery. Washing removes clotting proteins so dilutional coagulopathy may occur when massive volumes are transfused during operation; this may also occur after high-volume transfusion of bank blood. IAT involves an extracorporeal circulation and it might be expected that platelets would undergo sequestration and degranulation and develop transient dysfunction, as is seen after cardiopulmonary bypass; however, IAT does not cause a fall in platelet numbers due to sequestration. Although platelets from IAT reservoirs do not aggregate, recipients have normal *in vitro* platelet function and bleeding times compared with controls receiving bank blood[1]. No study has shown increased requirements for plasma or platelets with IAT.

IAT is effective. In a representative study only 10 per cent of patients undergoing coronary bypass surgery required homologous blood[2]. Reoperative cardiac surgery imposes particular demands and Dietrich *et al.* provided 60 per cent of the blood requirements in this group using IAT[3]. Aortic surgery is particularly suitable for IAT because shed blood pools in the peritoneal cavity and can be salvaged easily[4].

Orthopaedic surgeons in Europe and the USA have used IAT extensively, especially in revisional total hip arthroplasty and spinal instrumentation. Patients undergoing elective orthopaedic surgery are particularly suitable for predonation, which may be supplemented by IAT, and the infusion of wound drainage blood after operation is another effective method which is increasing in use. IAT is also effective in orthotopic liver transplantation, surgery for trauma, and ruptured ectopic pregnancy. Some words of caution are necessary. As fat and bone marrow are of similar density to red cells, centrifugal washing does not entirely remove them. Although there is reassuring clinical and experimental evidence that reinfusing blood contaminated with fat and marrow is safe, it is prudent to use extra washing and filtration during orthopaedic procedures. Washing may not remove other plasma components; one patient undergoing bilateral adrenalectomy for phaeochromocytoma experienced marked hypertension during the reinfusion of washed red cells. Washing may remove anaesthetic drugs such as fentanyl and this may be clinically significant.

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Tumour cell contamination and sepsis are, at present, relative contraindications to IAT. Cell washing does not remove cancer cells[5], but these do not appear to lead to increased metastasis in patients. Tumour cells infused intravenously would lodge in the pulmonary capillary bed; indeed, showers of tumour cells can be demonstrated in the portal and systemic venous circulation during cancer surgery. Similarly, peritoneovenous shunting for malignant ascites does not lead to pulmonary metastases despite the observation of non-invasive tumour emboli in some patients. Klimberg *et al.*[6] used a cell saver in 49 patients undergoing cystectomy, prostatectomy and nephrectomy for cancer, and the incidence and distribution of metastases were similar to those in unmatched controls having identical operations but with bank blood transfusion. Anxieties over the infusion of cancer cells may be ill founded; in curative surgery tumour margins should not be breached and in palliative procedures contamination may be less important. Pragmatism among trauma surgeons has resulted in the use of IAT in patients with contaminated surgical fields. Shock and sepsis are a particularly grave combination and adequately resuscitated patients tolerate bacteraemia better than those who are both hypovolaemic and septic. The only agreed absolute contraindication is faecal contamination, which (fortunately) blocks filters and makes IAT impossible.

The impetus for increasing use of IAT and other autologous blood techniques has been the human immunodeficiency virus (HIV) epidemic. Many data (and often emotive publicity) have come from the USA, where the prevalence of HIV infection is high. The risk of HIV seroconversion following a blood transfusion in the UK is about one in 1 000 000, but there is increasing awareness of the other infective risks, such as hepatitis C and retroviruses like human T lymphotropic viruses II and III, for which screening is not performed. The infective risk may be small but the transmitted diseases cause mortality and morbidity, and adversely affect public confidence, which may reduce the supply of bank blood. Blood transfusion also suppresses cell-mediated immunity, leads to increased perioperative infective complications[7] and may increase susceptibility to metastatic disease after surgery for cancer. The link between blood transfusion and cancer recurrence is not proven, but there is probably enough evidence to advocate a reduction in unnecessary exposure to donor blood.

The cost of IAT must be determined accurately if it is to compete with other methods; a recent cost analysis found it to be comparable to the use of bank blood[8]. However, the price of bank blood has since increased by 30 per cent. If a cell saver is used, the crossmatch order can be reduced, and in aortic surgery this could be a reduction from 8 to 2 units: a saving of over £350 per case. The National Blood Transfusion Service (NBTS) recognizes that IAT is effective and relevant, but there has been little progress in its implementation. Important issues are at stake, especially the protection of red cell and plasma product supplies. IAT should be administered and controlled by the NBTS as a complementary rather than competing service, but there is a financial barrier to development. Government recognition and central funding for this important advance are long overdue.

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Crohn's disease and nutrition

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Malnutrition was included by Crohn as one of the features of the new disease he described. Most patients with Crohn's disease are malnourished even if their disease is not active. Nutritional factors may be implicated in the aetiology of the disease, but this remains unproven. The role of nutritional support and therapy is discussed and it is suggested that improving the patient's nutritional status may have a primary therapeutic as well as a supportive role in the treatment of the disease.

Crohn's disease is a chronic, transmural, inflammatory disorder of the alimentary tract, manifested by marked ill-health, gastrointestinal symptoms and, sometimes, life-threatening complications[1]. It is more common in northern Europe and North America than elsewhere in the world[2]. The highest reported incidence to date is 8·3 per 100 000 population from Cardiff, and this is still increasing[3]. It is a disease that affects the young more than the elderly and females more than males[4,5], although this latter trend has only been noted in recent years[6]. It is a major cause of illness in the young. Since there is no known cure, they face a lifetime of illness, steroids and surgery.

Nutrition is intrinsically linked with Crohn's disease. Nutritional factors have been suggested as possible causes of the disease[7]; malnutrition and nutritional deficiencies are common in patients[8,9]; and nutritional therapy (both enteral and intravenous) has been advocated both as primary and as adjunctive treatment[9–11]. Crohn's disease and its surgery are now the commonest cause of the short gut syndrome[12] and many affected patients require long-term home parenteral nutrition[13]. Clearly, it is important to understand the role that nutrition plays in this disease.

Nutritional factors in the aetiology of Crohn's disease

Many factors have been implicated in the aetiology of Crohn's disease. It is commoner in certain parts of the world[2], in certain races[14,15] and in siblings of affected individuals[16]. Oral contraceptive users[17] and smokers[7] also have an increased risk of developing the condition.

Refined carbohydrates are a risk factor in the development of Crohn's disease[18]. This risk is independent of any increased risk from smoking[19]; non-smokers with the disease consume more sugar than smokers with the disease. Newly diagnosed patients have twice the 'normal' intake of refined sugar. The relative risk of developing Crohn's disease with a high sugar intake has been calculated on two occasions at 3·4 and 4·6, respectively[20,19]. Whether increased sugar intake is a cause or a consequence of the disease is much argued[18,19]. Several possible mechanisms whereby sugar may be implicated as a cause have been put forward, but none is proven[18]. It may also be argued, because Crohn's disease is extremely rare in countries such as Saudi Arabia and Morocco despite a large indigenous intake of sugar[21], that sugar consumption is either a consequence of the disease or that factors in addition to sugar are necessary for its development.

A close correlation has also been found between the incidence of Crohn's disease and the national consumption of margarine[22]. Further evidence for this hypothesis comes from Germany, where a retrospective analysis of diet before the onset of the disease has been performed[23]. Conversely, vegetables and fruit seem to have a protective effect[7,18].

Another theory involving diet in the aetiology of Crohn's disease is that the gut has an abnormal immunological reaction to a dietary constituent, and that this reaction is in some way the cause of the disease. Crohn's disease has long been suspected of having an immunological component, both because of its association with known immunologically mediated conditions and because of its favourable therapeutic response to steroids. Changes have been shown in both humoral and cellular immunity in affected patients, but these are probably non-specific and secondary to the disease process. There is no evidence that they have a primary role in causing Crohn's disease. Similarly, earlier hypotheses of gut allergic reactions to food allergens have not been substantiated[18,21].

Malnutrition in Crohn's disease

Malnutrition affects up to 50 per cent of surgical patients[24] and is frequently underdiagnosed[25]. Surgical diseases predispose towards protein-calorie malnutrition, and this is particularly the case with Crohn's disease. The reasons for this and the main mechanisms are shown in *Table 1*. These may cause malnutrition either singly or in combination, but a factor that is responsible for a particular nutritional deficiency may have very little responsibility for another, even in the same individual. Patients who are otherwise well nourished may become deficient in one or more nutrients. On the other hand, undernourished patients are at risk of developing multiple deficiencies. Reduced food intake, active inflammation and enteric nutrient loss are probably the most important causes.

Table 1 *The pathogenesis of malnutrition in Crohn's disease*

Method	Reason
Reduced food intake	Anorexia Fear of abdominal pain after eating
Increased requirements and decreased synthesis	Active inflammation Sepsis
Enteric loss of nutrients	Exudation from intestinal mucosa Interrupted enterohepatic circulation
Malabsorption	Loss of absorptive surface from disease or surgery Stagnant loop syndrome (from strictures, fistulae or surgical blind loops) Mucosal cell disease Lymphangiectasia
Miscellaneous	Rapid gastrointestinal transit Effects of medical therapy Effects of parenteral nutrition without trace element supplements

Adapted from Harries and Heatley[8] and Driscoll and Rosenberg[9]

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Many patients have excessive protein loss from the bowel and this is associated with vitamin and calorie malabsorption[26].

Weight loss has been regarded as a predominant feature of Crohn's disease ever since it was first described[27], and occurs in 70–80 per cent of patients[28]. In one study, 20 per cent of patients without active disease were more than 10 per cent below their ideal weight[29]; this study also found they had a more abnormal anthropometric profile than an analogous group with ulcerative colitis.

Carbohydrate absorption appears to be unhindered but fat and protein absorption are decreased, the latter resulting in specific amino acid deficiencies[8]. Affected patients are often also hypoalbuminaemic. Indeed, hypoalbuminaemia is not uncommon and, while intestinal protein loss, reduced hepatic protein synthesis, malabsorption and anorexia all play a role, hypoalbuminaemia results predominantly from increased catabolism and decreased synthesis due to the inflammatory process. Serum albumin level is more a marker of disease activity than of nutritional status. Decreased absorption of fat may be responsible for decreased absorption of calcium, magnesium and zinc[30].

Anaemia is also common and may be caused by either iron, folic acid or vitamin B_{12} deficiency, or it may occur simply as a result of chronic inflammation. Other specific deficiencies are: electrolytes (particularly magnesium), vitamin C (there appears to be an increased demand), vitamins D and K (owing to the disrupted enterohepatic circulation[31]), and trace metals (in particular zinc and selenium). Subclinical deficiencies of these are more common than the classical overt manifestations.

In children, malnutrition may result in delay in growth and in sexual development[32]. It appears that this is due to caloric insufficiency superimposed on protein, mineral and vitamin deficiencies, and that once the disease is under control (either surgically or medically) nutritional replenishment allows growth to restart.

Evaluation of the malnutrition of Crohn's disease has, until recently, been performed using only anthropometric and biochemical techniques[29,33–35]. These reports all expressed similar general conclusions: (1) certain categories of patients are non-specifically malnourished, and (2) anthropometric measurements reflect this better than biochemical ones. Specific conclusions were (1) patients who do worse after surgery are those with the lowest muscle bulk before operation[33]; (2) those with diffuse small bowel involvement are the most malnourished[29]; (3) there is greater loss of muscle than fat, particularly in ileal and ileocolic disease[34]; and (4) protein undernutrition is more common in women while calorie undernutrition is more common in men (but these conclusions were based only on serum albumin and triceps skinfold measurements)[35].

Measurements of skinfolds and plasma proteins are widely available and easy to perform, but the results are more applicable to groups of patients than to individuals, the techniques are not reliable in following changes in body protein in individual patients over a short period of time[36]. Body composition techniques (in particular *in vivo* neutron activation analysis and tritiated water dilution) provide accurate measures of both the different body compartments and any changes that occur in them[37,38].

A study on body composition in 71 patients with Crohn's disease has recently shown that while these patients are malnourished with a moderately severe protein depletion (they had only 77 per cent of their predicted protein stores), they are not fat-depleted as a group[39]. Those studied were not all surgical patients or even hospital patients, but a combination of hospital inpatients and outpatients who had been referred for body composition assessment and who represented a spectrum of disease activity (nine had a Crohn's disease activity index <150). Even patients with inactive disease, unstressed and without significant weight loss, as a group, have significantly less protein than would be expected (87 per cent of that predicted). *Figure 1* shows the relationship of body composition of patients with Crohn's disease (both male and female) with site of disease[40]. Malnutrition is most severe in those patients with upper gastrointestinal involvement, while those with colonic disease have lost fat rather than protein. One other study of body composition in Crohn's disease has been performed using total body potassium as a measure of lean body-mass (and so, indirectly, of protein)[41]. This study confirmed the protein depletion; 11 of the 13 patients studied had a significantly depleted total body potassium.

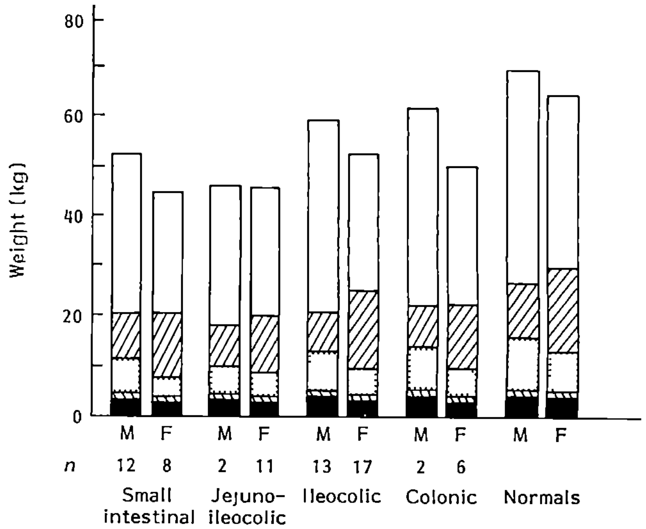

Figure 1 *Body composition analysis of 71 patients with Crohn's disease at different sites, compared with the 'normal' reference of a 70-kg man and a 65-kg woman. This shows protein depletion in all groups with a relative sparing of fat (except in colonic disease) when compared with normal.* ■, *Mineral;* ▧, *glycogen,* ⬚, *protein,* ▨, *fat;* □, *water. Between the groups, using analysis of variance, the differences in fat are significant in men and the differences in protein are significant in women* ($P < 0.05$)

Patients with Crohn's disease certainly lose protein from their gastrointestinal tract and the amount correlates well with the severity of their disease[42]. Perhaps such patients attempt to counter this protein loss by increasing their intake of calories as well as their intake of protein. These calories are well absorbed, and in those with solely upper gastrointestinal involvement only protein is lost back into the gut. This would explain the relative sparing of fat while protein is being lost[34,39].

Nutrition as adjunctive therapy

Nutritional therapy has a role as adjunctive treatment in Crohn's disease: (1) simply to improve nutritional status; (2) to ensure bowel rest when treating exacerbations of the disease, (3) in the treatment of postoperative fistulae; and (4) in the long-term management of short bowel syndrome.

Improving nutritional status

Dietary manipulation is the first stage in nutritional replenishment. Dietary advice alone can reduce symptoms[43]; a reduction in dietary bulk or in the amount of fat may reduce the severity of diarrhoea[26]. However, once these restrictions become necessary it is important to replace the fibre or fat with other foods to ensure an adequate supply of calories, protein, minerals and vitamins. Carbohydrates form an easily absorbed source of calories in these patients, but a high proportion of protein is required to maintain or restore weight, and many patients require additional multivitamin supplements.

Nutritional supplementation may be achieved using liquid diets which contain hydrosylated protein and a carbohydrate calorie source, or elemental diets which contain amino acids in place of protein, in addition to an oral diet. The elemental diets may allow easier absorption but they are often unpalatable to drink. Consequently, they are often given through nasogastric fine-bore feeding tubes, most patients can tolerate about 2 litres per day in this way. In general, nutritional problems due to Crohn's disease are amenable to treatment with some form of oral or enteral feeding[44].

Occasionally, intravenous nutrition (IVN) is required to effect nutritional repletion in patients with Crohn's disease[10]. A number of studies have found that IVN improves nutritional status, as measured by an improved sense of well-being, weight gain and a positive nitrogen balance[9]. Such nutritional repletion helps prepare patients for surgery and reduces complications after operation[45,46]. While IVN does not cause protein gain in patients with active Crohn's disease, it prevents further protein loss[47]. The effect of enteral nutrition is similar[48], and the satisfactory administration of either IVN or enteral nutrition should cause an improvement in physiological function (e.g. in both skeletal and repiratory muscle function)[49,50].

Bowel rest

For the past 10 years IVN has been advocated to rest the bowel in Crohn's disease[5,45,51]. The hypothesis was that if the bowel was not stimulated it would heal more quickly, like any other inflamed surface[9]. However, this effect has often been overstated; in many cases the results are not sustained. One study of 115 patients treated with IVN and bowel rest found that only 24 had a remission such that they were spared surgery; the treatment was deemed a failure in 50 patients and 57 had complications of their treatment[51].

Other studies have shown no primary therapeutic effect of IVN[47], and one has shown that IVN alone was no better than IVN with free access to food[52]. A recent major randomized multicentre study may have ended the argument by showing that bowel rest was less important than nutritional support[53]. This paper has led some to predict the demise of IVN for this indication, but this is probably an excessive reaction[54].

Crohn's fistulae

Enterocutaneous fistulae in Crohn's disease are of two types[55,56]. Type 1 fistulae arise from an area of intestine with active Crohn's disease and type 2 fistulae occur after operation from a site of anastomosis. Type 1 fistulae usually require surgery if they are to heal, whereas those of type 2 may frequently be cured by bowel rest and nutritional support[55–57]. This nutrition will usually be in the form of IVN, but with more distal fistulae an elemental diet may suffice.

Short bowel syndrome

Patients sometimes have many operations to resect areas of inflamed or strictured intestine. Surgery for Crohn's disease has become more conservative[58] but, even so, many patients are left with short bowel syndrome (Crohn's disease is now the commonest cause of this condition[12]). They may require long-term nutritional support, either in the form of home enteral nutrition[59] or, more commonly, home parenteral nutrition[44].

Home parenteral nutrition in the UK and Ireland has been carefully audited, and it has been shown that those requiring this treatment have a good quality of life[60]. Patients with Crohn's disease on home parenteral nutrition have lower mortality and morbidity rates and a better quality of life than other patients on this form of treatment[13,61]. About half require it for periods of 6–12 months (to allow adaptation, for closure of fistulae, or between operations in staged surgery for complicated fistulae, abscesses etc); the others require home parenteral nutrition for life[13].

Nutrition as primary therapy

Nutrition, particularly IVN, has been advocated as a primary treatment for Crohn's disease It was purported to act by resting the bowel but (as discussed above) this has been challenged[47] since 1980 and has now been effectively disproved in the multicentre trial from North America[53]. While IVN appears to have no primary therapeutic role in the treatment of Crohn's disease, elemental diets are now advocated in this context.

There are three studies worth noting in this respect. In a trial of 21 patients randomized to receive an elemental diet or steroids, the former proved as good as steroids in inducing remission[11]. A smaller randomized study of six patients showed that both steroids and an elemental diet induce remission and increase plasma amino acid flux[62]. Those on steroids lost a mean of 363 g protein over 1 week of the study, emphasizing the need for such patients to receive nutritional support. The third study compared an elemental with a polymeric diet, instead of steroids, in 30 randomized patients[63]. Patients receiving the elemental diet had a significantly higher remission rate than those on a polymeric diet

Factors felt to be involved in this primary role for elemental diets are: the decreased antigenic load of the elemental diet causes less stimulation of the inflamed intestine[63]; the glutamine contained in elemental diets is readily available for the small intestinal mucosa, where it is the primary energy source and essential for mucosal repair and regeneration[64]; and the improvement in nutritional support[62,63]. In a cross-over study of 28 patients, Harries *et al.*[65] showed that nutritional supplementation decreases serum orosomucoids and raises T lymphocyte levels. In this regard the findings of the multicentre North American trial[53] are relevant. This trial showed that nutritional support, independent of 'gut rest', facilitates remission in a number of steroid-resistant patients with Crohn's disease. Giaffer *et al.*[63] also explained remissions in their polymeric fed patients on the basis of improved nutrition.

It is suggested that improved nutrition may be the key factor in clinical improvement[66]. If this is so, then both IVN and enteral nutrition have a primary role to play in treatment.

Conclusion

Nutrition – the major function of the small intestine – is intimately involved with Crohn's disease. Whether nutritional factors have a role in the aetiology of the disease (either primarily or secondarily by initiating an abnormal allergenic response) remains unproven. Patients are certainly malnourished, particularly with regard to protein, and this is true even when their disease is in remission The causes of this malnutrition are many. enteric loss of protein, increased catabolism and reduced intake are probably the major contributors.

Nutrition as therapy for Crohn's disease remains controversial. It is accepted that IVN is of benefit in supporting those few patients with intestinal failure. Elemental diets are as good as steroids at inducing remission and there is a growing belief that by improving nutritional status significant remission may be induced. Consequently, both enteral nutrition and IVN may be primary therapeutic manoeuvres in this disease; the addition of glutamine to IVN may prove worthwhile. Certainly, both enteral nutrition and IVN have major supportive roles in preventing further protein loss in these patients and in improving their physiological function.

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Assessment of quality of life in surgery

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The concept of patients' quality of life is assuming increasing importance in modern medicine and surgery. Interventions are increasingly being assessed in terms of their impact on such areas of functioning as mobility, mood, cognitive function, ability to fulfil occupational and social roles, and general life satisfaction. This paper discusses the theoretical underpinnings of the quality-of-life paradigm and its practical relevance for modern surgery.

The concept of quality of life

Quantity and quality of life

Advances in the clinical sciences this century have resulted in an impressive range of diagnostic procedures, therapies, drugs and surgical techniques which have revolutionized the management of heretofore fatal conditions. There is still a school of thought which holds that survival is the be-all and end-all of human existence, and therefore clinical practice must always strive towards that objective. Priority, the argument runs, must be given to life-threatening situations, and only when these have been dealt with should we worry about quality of life. However, because people care about both their life expectancy and the future quality of their lives, it has become increasingly obvious that we must consider both as important. Facing the death penalty in an Athenian court, Socrates informed his judges that he feared some things more than death It was not life itself but the quality of that life that was important. In modern times, the work of Torrance[1] has shown that there are situations in which people will trade some life expectancy to improve the quality of their lives, and others in which treatment will be refused because the improvement in quality of life is not worth the risks.

In the 1940s several important papers were published which signalled a shift in the way we would come to look upon health and evaluate medical and surgical interventions. In 1947 the World Health Organization[2] introduced a broadened definition of health as 'a state of complete physical, mental and social well-being and not merely the absence of disease'. Some years later Karnofsky and Burchenal[3], in a classic study, outlined the basic criteria necessary for evaluation of new chemotherapeutic agents. These included not only traditional indicators of therapeutic processes such as survival and objective response, but also more qualitative parameters such as performance status, improved mood, reduction in symptom level and a sense of 'well-being', parameters that today would be classified under the heading 'quality of life' Despite the lack of conceptual agreement, quality-of-life variables have assumed ever-increasing importance in modern medicine, especially in the assessment of patients with chronic disease. A search of *Index Medicus* for papers using the major keywords 'quality of life' revealed that the annual number of published papers increased from 207 in 1980 to 846 in 1990.

A theory of quality of life

All good research should be underpinned by a sound theoretical formulation and some efforts have been made to develop theoretical models of quality of life. It has been proposed that persons are best viewed as lives lived with some degree of coherence; a human person is a life lived according to a human plan. It is the plan of life and the inter-related purposes of a person that give his or her life the unity and meaning it has. When pushed to say who we are, we reflect on our aims and upon the causes and principles with which we identify. We give an account of ourselves when we say what we did, or are doing, or intend to do with our lives[4].

Features of human life can be judged by their effect on the life plan. This view helps to explain why some features of human life are considered good while others are considered evil Intelligence, stamina, mobility and good health contribute to the realization of human plans. Features of life such as pursuit of one's vocation, the practice of one's art, the enjoyment of one's special pleasures and talents are evidence that the plan is being advanced. Some qualities of human life, however, hinder or block the pursuit of a person's life plan. disease, confinement to bed or to an institution, mental instability, fear and pain.

A similar view is that quality of life is reflected by the differences beween a person's hopes and expectations (life plan) and that individual's present experience. It is therefore dependent on the individual's past experience, present lifestyle, and hopes and ambitions for the future. The gap between hopes and realities may be narrowed either by improving the patient's functions through treatment, or by reducing expectations through informed understanding of the limitations of their disease and acceptance of the risks involved with treatment in relation to expected benefits[5].

What should be assessed?

Theoretical models such as those outlined above provide the basis for the scientific study of quality of life. One must assess whether a treatment, apart from its direct biological impact or its impact on longevity, produces the features that mark the fulfilment of plans and ambitions or the features that thwart such plans and ambitions, and the degree of each It follows that we will be concerned with features such as: Is the patient free or freer from pain? Can she return to work? Does she return to work? Is there more pleasure in his life? Is there freedom from depression and anxiety? Is he experiencing a satisfactory sex life? To what extent is she satisfied with her life in general?

Quality of life is a multidimensional construct and there are a variety of approaches to its measurement. Before embarking on a quality-of-life study one must decide on the answers to a number of key questions, the most important of which is 'What should be measured?' There is general agreement that studies on health-related quality of life should assess functioning in a number of important domains: physical functioning including somatic sensations such as physical symptoms and pain; psychological functioning including concentration and mood;

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social (including sexual) functioning; and finally occupational status. Some studies, particularly in the USA, include an assessment of economic status. A variety of standardized questionnaires is now available which assess quality of life across some or all of these domains. One of the more reliable and widely used general measures of quality of life is the Nottingham Health Profile (NHP)[6]. This is a questionnaire which assesses mobility, pain, sleep, energy, and social and emotional function as well as the impact of a disease on work, home and social life, sexual functioning, and leisure time.

Quality of life and surgery

Quality of life after surgery has been considered sporadically in the surgical literature since the turn of the century However, it has tended to be of secondary importance to the greater emphasis placed on the traditional outcome measures: mortality, morbidity, and operative complications. Recent interest in quality of life probably reflects the changing pattern of surgical diseases and the evolution of operative procedures. The improvements in anaesthetic techniques, the application of antibiotics, and advances in nutrition and other supportive measures have significantly reduced mortality and morbidity rates, thus decreasing their utility as indicators of outcome. Consequently, the success of an operation must be evaluated by means of other criteria. Relief of the patient's symptoms and overall satisfaction with the operation are often the important outcome measures. The number of surgical papers in which quality of life was a major focus increased from 11 in 1980 to 67 in 1990, and surgical papers which made mention of quality of life in the abstract increased from 21 per year to 138 per year over the same period. However, when one considers that the annual number of papers containing the term 'surgery' in the title or abstract has increased from 5608 to 13 007 in the same period, the modest increase in research interest in quality of life is placed in perspective.

Applications of quality-of-life assessments in surgery

Quality-of-life assessments may be applied in surgical settings to assess outcomes, to compare treatment options, to monitor and improve the quality of care, to aid in the selection of patients, to aid policy decision-making and resource allocation, as well as to describe the functional and psychological problems facing surgical patients.

Assessing outcome

Changes in the pattern of surgical diseases and the development of new techniques have increased the requirement to assess the outcome of surgery in the most rigorous manner possible The application of validated and reliable quality-of-life measures can produce dramatic evidence of the value of surgical interventions. For example, the Coronary Artery Surgery Study[7] showed that, while no significant surgical benefits were found in terms of mortality, survival and myocardial infarction rates, surgery significantly improved patients' quality of life. In a recent prospective study[8] the NHP was used to demonstrate the improvement in quality of life following coronary artery bypass surgery in a sample of 100 patients treated at Papworth Hospital in the UK. The NHP has also been used to demonstrate the improvement in patients' quality of life following heart transplantation[9]. Recently Lowe *et al.*[10], again using the NHP, demonstrated the improvement in patients' quality of life following liver transplant surgery in 81 adult patients treated in the Cambridge/King's College Hospital joint programme. The majority of patients were from the UK or Ireland and were within 2 years of transplantation. Findings indicated problems with physical mobility and sleep, but there was a halving in emotional problems compared with community-based norms Scores on energy, pain and social isolation factors were similar to normal scores. Data such as these show the value of using scales for which normative information is available.

Comparing treatment options

Quality-of-life considerations can be important in comparing treatment options and in assisting both patients and healthcare professionals to decide between treatments From the patient's point of view, quality-of-life considerations may be of paramount importance in reaching such a decision. For example, it has recently been demonstrated that 23 patients of a series of 50 with advanced prostatic cancer chose to undergo orchidectomy as opposed to the equally effective hormone treatment. Orchidectomy was more likely to be chosen by inpatients who felt that the convenience of the procedure, with minimal disruption in quality of life, was an important factor in favour of the surgical option[11].

Monitoring and improving the quality of care

When new surgical techniques are developed for the express purpose of improving quality of life without necessarily improving survival rates or decreasing morbidity, quality-of-life assessment is crucial. An example was the development of the Kock continent ileostomy, and later the ileal reservoir and ileoanal anastomosis, to overcome the difficulties some patients had in adjusting to the conventional Brooke ileostomy[12].

Selecting patients for surgery

Quality-of-life measures may play an increasingly important role in selecting patients for surgical procedures and in managing queues, particularly in situations where resources are limited. While further research is needed, it does appear that quality-of-life scales may have value in predicting the outcome of surgery. Evans *et al.*[13] found that functional impairment before heart transplantation, measured by the Karnofsky index, correlated strongly with survival after transplantation. An individual who scored a maximum impairment level of 10 was found to be at nearly four times greater risk of death than an individual who scored 1 on the impairment scale. At Papworth Hospital, surgeons identify two levels of acceptance on to the heart transplant programme. provisional and definite. If at the time of assessment the patient is not considered ill enough to warrant transplantation he or she is put on a provisional list and is accepted definitely only if further deterioration occurs. All scales on the NHP have been shown to discriminate between provisional and definite candidates[9]. The strong correlation between the NHP and clinical judgement and the apparent power of the NHP to discriminate between different expected prognoses for accepted patients raises the possibility that it could be used as part of a screening procedure or in the management of queue priority

Policy decisions and resource allocation

In the UK there is increasing use of the quality-of-life concept combined with economic indices in the priority assessment of healthcare demands and the distribution of resources[14,15]. The commonest approach combines measures of quality and quantity of life into one index, the quality-adjusted life year (QALY). A QALY represents 1 year of healthy life expectancy. One year of unhealthy life is worth correspondingly less than one QALY. A high priority healthcare activity is one where the cost per QALY is low, and a low priority activity is one where the cost per QALY is high. The use of QALYs to determine the effectiveness of alternative care strategies and thereby assist in the choice of treatments may generally be regarded as unexceptionable, but their deployment to determine who should and who should not receive treatment for reasons of cost has been roundly rejected by a number of commentators on ethical, philosophical and methodological grounds[16–19]. A crucial problem is that the meaning of the QALY is that given to it by the economists who formulate, administer and interpret it, rather than the individual whose health is assessed by it. A major question is whether a QALY actually represents the real desires of individuals, particularly patients

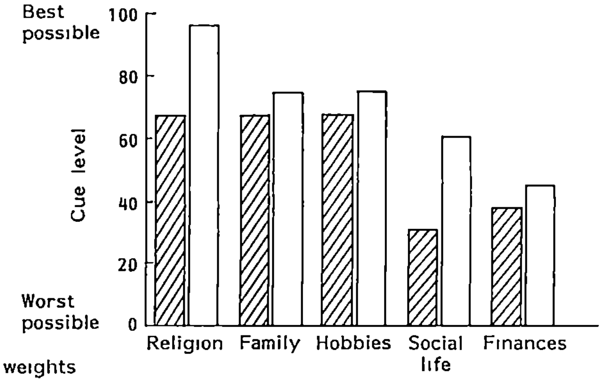
Quality-of-life measurement for the individual

Improving the quality of a patient's life will involve attention to some elements that can be prized by us all since they will tend to maximize the realization of life plans. However, since an individual's experiences, ambitions and plans are individual to him or her, some elements will be important to a particular degree for particular patients[4]. Most available quality-of-life measures, including QALYs, impose an external value system on patients, using standardized formats, questions and weightings of individual components of quality of life, which are usually derived from grouped data. The question of the relevance of such measures to the situation of the individual patient with his or her unique perspective on their own quality of life has not been widely addressed. Specific goals or behaviours important to an individual's quality of life, such as attending religious services or duck shooting, are not represented adequately by broad questions about physical mobility or general health. Even if this were not the case, apparently similar behaviours do not have the same significance for all individuals desiring to experience them. Neither do events or functions necessarily retain the same salience for a given individual with the passage of time or indeed over the course of an illness. To paraphrase Aristotle:

> '... when it comes to saying in what happiness consists, opinions differ, and the generality of mankind take it to be something obvious and familiar, like pleasure or money or eminence, and there are various other views, and often the same person actually changes his opinion. When he falls ill he says it is his health, and when he is hard up he has that it is money.'
>
> (Aristotle (384–322 BC) *Ethica Nichomachea*)

In collaboration with teams in Copenhagen and Basel, the team at the Royal College of Surgeons in Ireland has been developing a method based on the technique of judgement analysis as a means of incorporating the individual patient's perspective into the measurement of quality of life[20]. Patients nominate the five areas of life which they consider most important to the overall quality of their lives. They rate their current status in each area or cue against a vertical visual analogue scale, labelled at the upper and lower extremities by the terms 'as good as could possibly be' and 'as bad as could possibly be', respectively. A profile is generated by the interviewer using bar charts. Patients are then asked to consider their profile and rate their global quality of life on a horizontal visual analogue scale. At this stage of the procedure we know which areas of life are most important to the patient and his or her level of functioning in each of these areas. To quantify the relative weight attached to each cue, 30 randomly generated profiles of hypothetical subjects labelled using the five chosen cues are presented and the subject is asked to judge the global quality of life for each profile. By means of multiple regression it is possible to calculate the weight attached to each cue in making the global judgement. A global score can be derived by multiplying the relevant cue weights by the individual's current self-rating and summing across the five cues. Thus the global score incorporates the individual's current status on each of the five salient variables as well as the relative importance of those particular variables to him or her.

One of our studies compared the change in quality of life in 20 patients with osteoarthritis before and 6 months after unilateral hip replacement surgery with that of 20 matched controls assessed over a similar timescale[21]. Considering the case of a 76-year-old woman (*Figure 1*) who underwent unilateral hip replacement after 6 years of continuous pain with a Harris hip rating of 26, we see that she nominated religion, family, hobbies, social life and finances as the most important areas of her life, which gave a global score of 55·8. This was increased to 72·6 at 6 months after hip replacement surgery, with improvement in all areas. Notably, the relative importance of the five components as reflected in the derived weights also changed. Grouped data showed significant improvement in quality of life measured using the individual technique and, importantly, the quality of life of patients after operation exceeded that of healthy controls. I believe that a major focus in quality-of-life research for the 1990s will be an attempt to incorporate more fully the perspective of the individual patient into a standardized assessment.



Cue weights	Religion	Family	Hobbies	Social life	Finances
Before operation	0·37	0·23	0·06	0·28	0·06
After operation	0·19	0·39	0·18	0·04	0·20

Figure 1 *Application of individualized technique*[21] *to assess the impact of hip replacement surgery on the individual quality of life of an elderly patient Assessment was conducted before* (▨) *and 6 months after* (☐) *surgery. The cue weights are derived by judgement analysis and represent the importance of each area to the patient. The quality-of-life score is derived by multiplying the level of functioning in a particular area by the weight assigned to that area and summing the resultant multiples. score before operation 55·8; after operation 72·6*

Quality of life and surgery in the 1990s

It is likely that the need to assess surgical procedures in terms of their impact on overall quality of life will become increasingly important. Newer operations are being developed for the express purpose of improving quality of life without any improvement in survival rates or change in morbidity. Such procedures will have to be compared with conventional techniques to establish their value and role.

As indications for surgery expand, change in the assessment of surgical results is required. Failure of medical therapy is a not uncommon indication for surgery in gastrointestinal disease[12]. In cases such as this the success of the operation is determined by whether the patient is cured of their symptoms and whether quality of life is improved. Surgery is also being performed more frequently for prophylaxis or palliation, and in such applications quality of life is an essential component of assessment. Quality-of-life indices may also have a role in surgical audit, probably as an added dimension to the assessment of outcome, and they may prove to be particularly important in paediatric surgery where the potential impact of an intervention on the life plan is likely to be magnified by virtue of the young age of the patient.

As knowledge of and interest in medicine by lay people increase, patients and their families are participating more in decision-making, not only about when to operate, but also about whether to have an operation and which one to have. Patients are naturally reluctant to undergo surgery if its negative impact is greater than that of the disease and side-effects of medical therapy. When deciding about surgical procedures, quality-of-life issues and long-term outcome may be equally or more important to the patient as the complication rate. McLeod and Fazio[22], in a survey of patients with continent ileostomies, found that 94 per cent stated they would rather have revisionary surgery should complications occur than have a conventional ileostomy re-established.

The changes in the National Health Service in the UK, with the attempt to develop a competitive internal market, have sharply focused attention on 'value-for-money' assessment of interventions. Quality-of-life issues are likely to assume central importance in making such judgements. It would be unfortunate for patients and healthcare professionals alike if measurement techniques which failed to take account of the perceptions of individual patients became the standard by which resource allocation decisions were made. Those involved in quality-of-life studies often comment on what a valuable contribution to therapeutic judgements the eliciting of quality-of-life data proved to be, and how communication between the patients and practitioner may be enhanced. They have occasionally expressed some surprise at the low value some patients attach to some threatened aspects of quality of life and the high value attached to others, quite contrary to the practitioner's own expectations. In a well known study, Sugarbaker *et al.*[23] compared the impact of two treatments for sarcoma on quality of life with the expectation that limb-sparing surgery and irradiation would provide improved quality of life compared with amputation. The expectation was not confirmed by their findings, amputation having the lesser negative impact on patient quality of life

The new quality-of-life paradigm is a two-edged sword in that it demarcates the limits of conventional medicine and surgery but also liberates the whole range of health carers, professional and lay, to adopt the broadest possible therapeutic aims[24,25]. To quote Harvey Schipper[26], director of the World Health Organization's Collaborating Centre for Quality of Life Studies in Cancer:

> 'We tread on new and unfamiliar ground Quality of life studies will force us to come out from the comfort of technological medicine into a world that is less concrete and less controllable, but more human The relevance and validity of some of our most trusted measures will be reassessed. Out of it we will be better physicians, more sensitive to the vigour, complexity and adaptability of the human soul.'

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Knotting technique and suture materials

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Three groups of knots were examined using six no. 1 (metric 4) suture materials to identify the most effective and efficient knotting techniques. The three groups were the square or reef knot, the surgeon's knot and a double throw knot. Sequential single additional throws were added to these in order to determine when the strength of the knot reached the breaking force of the material, thus nullifying the need for additional throws. This strength was reached in all cases by a maximum of two additional throws. Suture materials examined were the non-absorbable monofilaments nylon and polypropylene, the absorbable monofilaments polyglyconate and polydioxanone and the braided materials polyglactin and polyglycolic acid, both coated. These were examined for their knot-holding capacity and breaking force to determine the best materials, which were polypropylene, polyglyconate and polyglycolic acid.

The tying of knots is as important as any aspect of surgery but there is a relative scarcity of quantitative research in this area As a result of this lack of information many techniques of knot tying are adopted that are not necessary. Concern regarding knot security appears to be greatest with the monofilament materials and, as a consequence, a variety of knotting techniques is employed. These include the addition of multiple throws to the initial knot and leaving long cut ends of suture material after completion of the knot, with or without burying them beneath previous sutures or in subcutaneous tissue. Both these practices result in excessive amounts of foreign material remaining within the wound and one method employed to prevent such excess in the subcutaneous tissue is to tie the knot on the undersurface of the closed layer. This is a poor solution because it is impossible to snug down the loose ends in opposite directions within the same plane as the basal threads, the prerequisite for tying secure square knots.

The aim of this study was to identify the holding capacities of different knots using a variety of suture materials, to identify the most effective knotting techniques, and thereby to eliminate unnecessary time-consuming practices. In addition, the tensile strengths of the suture materials were examined along with their individual characteristics.

Materials and methods

Six suture materials (seven types of suture) were examined, forming three distinct groups: absorbable, non-absorbable monofilament and braided In the non-absorbable monofilament group polypropylene (Prolene; Ethicon, Edinburgh, UK) and nylon (Dermalon, Davis and Geck, Gosport, UK and Ethilon; Ethicon) were examined, with two types of the nylon being included as it is probably the most widely used material for abdominal wall closure. Polydioxanone (PDS, Ethicon) and polyglyconate (Maxon, Davis and Geck) were examined from the absorbable monofilament group, and coated polyglycolic acid (Dexon; Davis and Geck) and polyglactin (Vicryl, Ethicon) represented the braided group. All materials examined were no. 1 size (metric 4).

The knots tested fell into three groups depending on the starting knot. These were the square or reef knot, the surgeon's knot and a repeat double throw knot which will be called the double knot. To each of these knots additional single throws, to a maximum of four, were added to form a new knot that was individually tested. Thus a total of 15 knots was tested (*Figure 1*). Slip knots or 'granny knots' were not included as these offer little security If they are used intentionally they should be further secured

In testing, the knot to be examined was formed between two strands of the suture material in question before an increasing distraction force was applied to the loose ends. This continued until the knot slipped or the material broke. Appropriate configuration was ensured before the knot was snugged down by hand against a constant force of 1N applied in opposite directions on the basal ends of the suture material ($1N = 1\ kg\ m\ s^{-2}$) All knots were tied by the same operator and were lubricated with water before testing to approximate more closely *in vivo* conditions. Each knot was tested ten times. If it demonstrated a variable holding capacity a further 20 tests were carried out. The force required for the knot to slip or the material to break was calculated in newtons. The knot-holding capacity, defined as the force required to cause the knot to slip, and the breaking force, defined as the force required to break the suture material, were calculated.

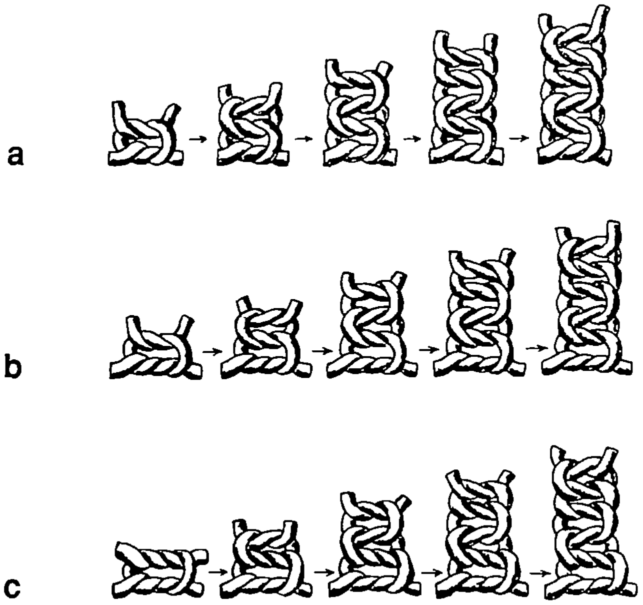

Figure 1 *The basic knots with additional throws*· **a** *square knot;* **b** *surgeon's knot,* **c** *double knot* © *R. P Brown*

Two additional characteristics of the suture material were examined. reliability of both the knot-holding capacity and breaking force, and the recomposure quality, defined as the ability of the material to reform knot configuration after initial slippage.

Results

The results are summarized in *Table 1*. The starting knot always had two throws, and the additional throws are represented in horizontal rows. The last figure in each row represents the breaking force. The knot-holding capacity increases rapidly as the number of throws increases until it equals the breaking force. Once this point is reached the addition of further throws

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Table 1 *Knot-holding capacities of seven suture materials using two, three or four throws*

	Square knot			Surgeon's knot			Double knot		
Suture material	2	3	4	2	3	4	2	3	4
Ethilon	5·0(0·8) [10·8]	25·1(2·2) [54·1]	45·9(3·7) [100]	6·3(0·8) [13·8]	28·2(4·8) [61·8]	45·4(3·9) [100]	22·4(2·8) [47·9]	46·8(4·0) [100]	
Dermalon	6·9(0·5) [16·1]	32·5(3·8) [77·1]	46·4(3·9) [100]	8·8(0·8) [19·7]	44·6(4·7) [100]		40·0(3·2) [100]		
Prolene	9·8(2·4) [19·9]	49·5(3·9) [100]		20·1(7·6) [37·2]	53·9(5·7) [100]		54·2(4·4) [100]		
Vicryl	25·4(2·4) [50·5]	50·4(3·8) [100]		21·3(3·1) [40·8]	52·0(2·5) [100]		53·5(3·3) [100]		
Dexon	59·1(2·0) [100]			59·1(2·1) [100]			60·4(3·6) [100]		
PDS	6·7(0·4) [11·1]	60·6(3·6) [100]		10·7(1·8) [17·4]	61·7(5·1) [100]		26·0(2·0) [43·0] 60·5(6·0) [100]	60·5(6·0) [100]	
Maxon	16·4(6·6) [20·2]	81·2(2·6) [100]		13·4(2·8) [16·3]	82·1(4·3) [100]		82·1(2·6) [100]		

Values of knot-holding capacities are mean(s.d.) in newtons. Values in square brackets are knot-holding capacity as a percentage of breaking force

to the knot results in no further increase in strength of the knot. In all groups this was reached by a maximum of two additional throws to the starting knot, i.e. four throws.

The square or reef knot

The breaking force of Dexon was reached without any additional throws. The nylon materials required two additional throws but all other materials required only one further throw.

The surgeon's knot

Again the breaking force for Dexon was reached without the need for additional throws, with one additional throw required for all other materials except Ethilon, which required two.

The double knot

For all suture materials except Ethilon and PDS the breaking force was reached with a double knot throw, Ethilon and PDS required an additional throw. Two sets of results were obtained for PDS for the double throw. Sometimes the breaking force was reached with this knot alone, but at other times the knot-holding capacity was approximately half of the breaking force, reaching it only with an additional throw. No determining factor for these two groups was found. The double throw knot, therefore, gave the greatest knot-holding capacity for all materials. However, if the parallel configuration of the two double throws was distorted by overtightening, it resulted in the knot-holding capacity being reduced to half of the breaking force, necessitating an additional throw for security.

Knotting properties of materials

Dexon demonstrated the greatest knot-holding capacity and did not require an additional throw for any of the knots tested. In this respect it proved superior to Vicryl, as well as demonstrating a greater breaking force. Similarly, Maxon proved superior to PDS in knot-holding capacity and in breaking force. Prolene proved to be the superior non-absorbable monofilament material, having a greater knot-holding capacity and a 20 per cent greater breaking force than nylon. Overall, of all the monofilament materials, Maxon proved to be the best in both its knot-holding capacity and breaking force.

Reliability

The reliability of the results of each material is represented by the standard deviation from the mean. Prolene and Maxon showed the greatest variation, but this was not great in relation to the overall knot-holding capacity and breaking forces.

Recomposure quality

The materials fell into two groups. In one group (including Ethilon, Dermalon, Prolene and PDS) knot slippage was followed immediately by total disruption of the knot. In the other group (Vicryl and Maxon) initial knot slippage was followed by knot recomposition; disruption was then resisted until a greater force was applied. This is important because if total disruption of the knot occurs this will happen regardless of supposed preventive measures, such as leaving long cut ends of suture material. Dexon slipped at no point, and therefore could not be categorized.

Discussion

It has been shown that knot-holding capacity reaches breaking force with all materials after addition of a maximum of two throws to any of the starting knots. This means that the addition of multiple throws to a knot is unnecessary. Leaving long uncut ends of suture material after tying is, consequently, also unnecessary. This is further borne out by examining the recomposure quality of the materials. By applying this knowledge, operating time may be shortened and excessive foreign material in the wound may be avoided. The choice of suture material group is made depending on the estimated time of wound healing but within groups some materials demonstrate superior qualities. In the non-absorbable monofilament group Prolene was preferred to nylon; in the absorbable monofilament group Maxon was preferred to PDS; Dexon was the better choice in the braided group.

However, it should be emphasized that these results apply only to no. 1 gauge material when the knots can be tied by pulling the loose ends in opposite directions. These conditions apply particularly to abdominal wound closure and should not be extrapolated to finer materials tied in the depths of a wound. Furthermore, the superior knot-holding capacity of the material may sometimes be a disadvantage, for instance when trying to secure knots down a deep cavity where a certain degree of knot slippage may be of advantage.

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Prediction of wound tensile strength: an experimental study

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Wound cell specimens were obtained using a Cellstic device after 24, 48 and 72 h healing time in guinea-pig skin wounds. Cell counts from these were compared with the tensile strength values of the same wounds 7, 14 or 21 days after operation. No single cell type was predictive of wound tensile strength, although absolute numbers of different cells and selected ratios of cell types on the second or third day after operation were more predictive. Absolute and proportional changes from day 1 to day 2 had the greatest predictive power with a mean error of 9·46 per cent (F = *13·6*, P < *0·0001*)*. The same regression model was predictive in animals with lower wound tensile strengths given perioperative hydrocortisone* (*3 mg/100 g*).

The sequence of events in connective tissue regeneration is similar in all mammals[1]. Repair of open wounds may be predicted by several methods in experimental animals and in humans[2–5]. Healing speed of closed incisional wounds is best determined by tensile strength measurement, which reflects the quality and speed of regeneration This method is, however, not suitable in humans. Because the prediction of healing speed in an incisional wound is of clinical importance experimental methods have been developed for studying human wound healing. Cellstic (Cellomeda, Turku, Finland) is composed of a standard rectangular piece of viscose cellulose sponge inside a silicone rubber tube[6,7]. Miniature polytetrafluoroethylene (GORE-TEX; W. L. Gore, Flagstaff, Arizona, USA) tubing was later used for the same purpose[8] A third method used an implant consisting of two polyvinyl alcohol sponges in a perforated silicone rubber tube[9] Human wound healing has been assessed by analysing *N*-terminal propeptide of type III procollagen from wound fluid[10].

The present study examined whether numbers of inflammatory cells in an incisional wound are predictive of the development of its tensile strength.

Materials and methods

Forty 3-month-old guinea-pigs were used, housed individually in cages and fed *ad libitum*. On the day of operation they weighed from 630 to 790 (mean 686) g Five animals were treated for 7 days before and after operation with hydrocortisone (Solu-Cortef, Upjohn, Kalamazoo, Michigan, USA) 3 mg/100 g intramuscularly Using spinal anaesthesia[11] and under sterile conditions four paramedian standard incisions of 3 cm each were made symmetrically on the dorsal skin of the animals. One end of a Cellstic test drain was left subcutaneously in each of the four wounds Cellstic test drains were composed of a standard piece of cellulose sponge (Absorpal; Dr Ingerfeld, Dusseldorf, Germany) 1 × 1 × 16 mm in size and weighing 9·4–9 6 (mean 9 50) mg, and Silastic tube (medical grade tubing no 602-235; Dow Corning, Midland, Michigan, USA). The other end of the drain was protected with a plastic tube to prevent damage and contamination (*Figure 1*). Wounds were closed in one layer with monofilament polypropylene sutures (4/0 Prolene; Ethicon, Sollentuna, Sweden).

The sutures and plastic tubes were protected by folding and suturing the skin from both sides over the wound Cellstic drains were removed 24, 48, 72 and 96 h after operation. On the seventh, 14th and 21st days after operation, under spinal anaesthesia and sterile conditions, an ellipsoid skin area with a healing wound in the centre was excised for tensile strength measurement This excision wound was closed immediately on days 7 and 14 with a continuous suture The thickness of the excised skin was measured on each side of the wound. Two strips, 10 mm in breadth and perpendicular to the wound, were cut from the middle of each wound for tensile strength measurement[12]

After the Cellstic drains had been withdrawn, the cells and cell aggregation centres were washed out by retrograde injection, cytocentrifuged at 1000 r p.m. for 7 min and stained with a May–Grunwald–Giemsa stain. Polymorphonuclear cells, lymphocytes, monocytes, macrophages and cells in cell aggregation centres were counted differentially[13]. The absolute numbers of cells after the first 24 h were designated· PMN_1 for polymorphonuclear leucocytes, LY_1 for lymphocytes, MO_1 for monocytes, MA_1 for macrophages and CAC_1 for cell aggregation centres. PMN_2 and PMN_3 were used for PMN cells after 48 and 72 h, respectively. The same type of indexing was used for other cell types Indices TS_7, TS_{14} and TS_{21} were used for measured tensile strength values of the seventh, 14th and 21st days after operation The best possible subset regression analysis (BMDP; BMDP Statistical Software, Los Angeles, California, USA) was used The tensile strength predictive value of inflammatory cells was examined by comparing the absolute numbers of cells harvested from the wound space of a given animal and their square root transformed ratios in the early phase (24, 48, 72 and 96 h) of wound healing with wound tensile strengths of later phases (7, 14 and 21 days).

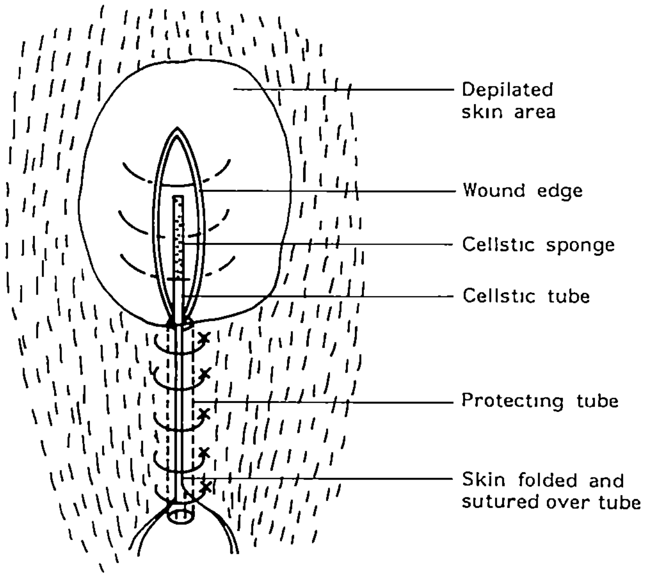

Figure 1 *Implantation scheme of the Cellstic device*

When wound infection in any of the four wounds (one case) or bacterial contamination of the Cellstic specimen (three cases) occurred, the animal was excluded from the study. The final results of all four Cellstic specimens per animal and corresponding tensile strength measurements were obtained from 36 animals. The cells harvested by a Cellstic sponge at 96 h showed increased cytolysis and could not be used for exact differential counts

Results

Original cell counts

Cell counts at 24 h did not allow reliable tensile strength

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prediction. The differential count of Cellstic cells at 48 h was more predictive and as reliable as prediction based on the differential count at 72 h for measured tensile strength on the seventh, 14th or 21st day after operation. Original cell counts at 24 h were predictive when combined with those at 48 h or 72 h in the same animal, expressing the speed of change in cell composition during precise time intervals.

The shorter the time of Cellstic implantation, the more uncertain was the prediction of wound tensile strength by Cellstic cell numbers. Prolongation of implantation time beyond 72 h did not improve the reliability of prediction because of increased cytolysis.

Original cell counts together with transformed ratios

By using $\mathrm{PMN_1}$, $\mathrm{MA_1}$, $\mathrm{PMN_2}$ and square root transformed ratios of $\mathrm{MO_1{:}PMN_1}$, $\mathrm{MA_2{:}LY_2}$ and $\mathrm{MA_2{:}MO_2}$, R^2 for $\mathrm{TS_7}$ was 83·0 per cent and the mean error from the measured $\mathrm{TS_7}$ values was 13 per cent. In animals treated with hydrocortisone the best estimated regression model for $\mathrm{TS_7}$ included original cell counts of $\mathrm{PMN_1}$, $\mathrm{MA_1}$, $\mathrm{PMN_2}$ and transformed ratios of $\mathrm{MO_1{:}PMN_1}$, $\mathrm{MA_2{:}LY_2}$ and $\mathrm{MA_2{:}MO_2}$ of which $\mathrm{MA_2{:}MO_2}$ contributed by 49 per cent to R^2. Despite remarkable reductions of tensile strength in hydrocortisone-treated animals, their $\mathrm{TS_7}$ (*Figure 2*) and $\mathrm{TS_{14}}$ (*Table 1*) values were predictable in the same way as tensile strength in untreated animals. By combining original numbers of Cellstic cells and their transformed mutual ratios at 24 and 72 h, as presented in *Table 2* and *Figure 3*, R^2 for $\mathrm{TS_{14}}$ increased to 83·6 per cent, mean error being about 9 5 per cent ($F = 13{\cdot}6$) and associated probability $P < 0{\cdot}0001$. The contribution of $\mathrm{MA_1{\cdot}LY_1}$ to R^2 was 53 per cent For $\mathrm{TS_{21}}$ no reliable prediction model with a cellular basis could be found.

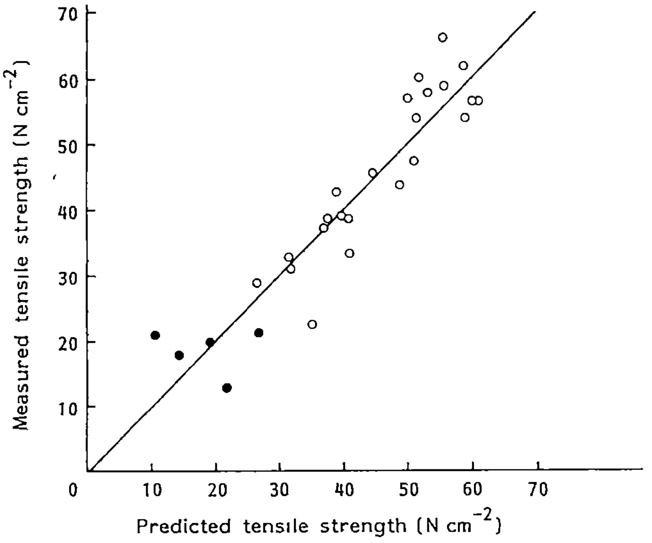

Figure 2 *Correlation between predicted and measured tensile strength on the seventh day after operation in control* (○) *and hydrocortisone-treated* (●) *guinea-pigs*

Table 1 *Comparison between observed and predicted wound tensile strengths in hydrocortisone-treated guinea-pigs at day 14*

Observed (N cm^{-2})	Predicted (N cm^{-2})	Difference Absolute (N cm^{-2})	Difference Percentage
39·25	38 70	0 55	1 4
39 20	42·56	−3·36	−8 6
37·70	37 17	0 53	1 4
31·40	27·97	3·43	10 9
33 25	34·13	−0·88	−2 6

Discussion

In primary wound healing, an adequate number of fibroblasts with normal function between the wound edges is needed for normal collagen accumulation, crosslinking and subsequent increase in wound tensile strength. The number of fibroblasts participating in wound repair is often an indirect measure of the development of wound strength. No studies have been published to show whether wound inflammatory cells, before the appearance of fibroblasts, are predictive of later tensile strength. This study addressed the question of how soon after wound infliction tensile strength can be predicted.

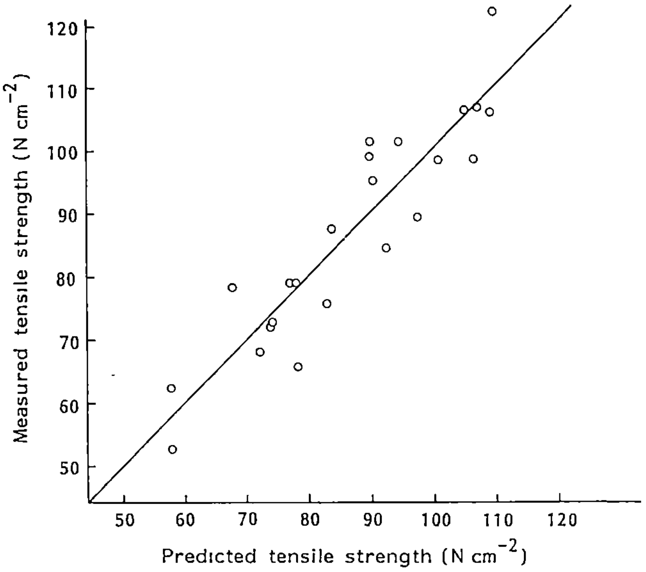

Figure 3 *Correlation between predicted and measured tensile strength on the 14th day after operation*

Table 2 *Best model for tensile strength on the 14th day after operation based on the differential count of Cellstic cells on days 1 and 3* (*Intercept 1719, standard error 179 9, standard coefficient 9·74*)

Variable	Regression coefficient	Standard error	Standard coefficient	Tolerance	Contribution to R^2
$\mathrm{PMN_1}$	−0·76	0 25	−0 39	0 65	0·10
$\mathrm{PMN_3}$	−0·28	0·14	−0·25	0 65	0·04
$\mathrm{MA_3}$	−2·41	0 60	−0·45	0·81	0 16
$\mathrm{CAC_3}$	12 78	6 58	−0·20	0 93	0 04
$\mathrm{MA_1{:}LY_1}$	−31 31	4 35	−0·77	0 90	0 53
$\mathrm{LY_3{:}PMN_3}$	10 29	2·97	0 47	0·55	0·12

PMN, polymorphonuclear leucocytes; MA, macrophages; CAC, cell aggregation centres, LY, lymphocytes Subscripts indicate days after operation

Its results show that such prediction is possible from the absolute numbers of inflammatory cells and their mutual ratios as early as 48 h after wounding. This becomes more apparent when the results from two subsequent time intervals are combined. This is not surprising, because each interval reveals a change in cellular patterns. The occurrence of PMN, lymphocytes and red blood cells is insufficient to give any reliable information for prediction of subsequent tensile strength. The appearance of the first monocytes and macrophages is decisive for the progress of wound healing and after this the prediction of wound healing is greatly facilitated[14]. Predictive power of the inflammatory cells did not extend to TS_{21}, presumably due to several factors (e g. collagen maturation) not related to early cell composition.

If methods were available to show the multipotent function of wound inflammatory cells and this information could be combined with data on wound cell numbers and ratios, tensile strength could probably be predicted more precisely The lag or latent phase of wound healing has gained new significance It is a period of inflammation, but its high predictive power for tensile strength has not been understood. Early detection of abnormalities in wound cell composition is a forewarning of disturbed wound healing. The results show that changes in wound cell composition within a short interval, both in normal and hydrocortisone-treated animals, predict later tensile strength as early as the inflammatory phase of wound healing.

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Announcement

Eurosurgery 1992

The 2nd European Congress of Surgery under the auspices of Eurosurgery/Eurochirurgie will take place in Brussels in June 1992. This meeting will pursue the aims of Eurosurgery/Eurochirurgie to promote research and training in surgery.

There will be national sessions sponsored by the associations of surgery of all participating nations. Areas of topical interest will be covered in symposia and free paper sessions in areas of general interest and in the specialist fields of abdominal, thoracic, transplantation, trauma, paediatric, endocrine, plastic and vascular surgery. There will be several symposia related to surgical training.

The abstracts of the free paper communications will be published in a special supplement of *The British Journal of Surgery*.

Further details and registration forms may be obtained from the Congress of Secretariat Eurosurgery 1992, Brussels International Trade Fair, Place de Belgique, B1020 Brussels, Belgium. Telephone: 322 477 0457. Facsimile: 322 477 0391.

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Adenomatous goitre: therapeutic strategy, postoperative outcome, and study of epidermal growth factor receptor

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A total of 377 patients with histologically proven adenomatous goitre was operated on, 34 as a second operation, and assessed for postoperative outcome (including the incidence of unsuspected malignancy) and immunohistochemical localization of epidermal growth factor receptor. In primary surgery, enucleation of all the nodules was carried out. Patients requiring reoperation showed multicystic degenerate nodules involving one or both lobes. A coexistent cancer was observed in 18 patients (4·8 per cent). The immunohistochemically detected expression of epidermal growth factor receptor in adenomatous goitre was more evident in patients with multinodular lesions. Near-total lobectomy of the involved side(s) is desirable for the prevention of recurrence and complications after operation.

Adenomatous goitre is a benign nodular lesion of the thyroid gland considered to be due to genetic differences in follicular cells[1]. It may be influenced by iodine deficiency and other factors. Histopathologically the lesion is benign and characterized by the coexistence of hyperplasia and various retrogressive changes: cyst formation, softening, necrosis, old and recent haemorrhage, and calcification[2].

In Japan, surgery has been the primary treatment although suppression of endogenous thyroid-stimulating hormone (TSH) secretion with thyroid hormones is becoming more widely utilized[3]. It is not clear whether adenomatous goitres will regress on thyroid hormone therapy[3,4] and there is no general agreement over the appropriate therapeutic approach.

In this study clinical and operative findings in patients were correlated with the outcome of surgery and the incidence of cancer. The presence of epidermal growth factor receptor was also investigated using immunohistochemical techniques.

Patients and methods

A total of 377 patients with histopathologically proven adenomatous goitre was treated surgically from 1973 to 1987 These patients comprised 15 per cent of those undergoing surgery for thyroid disease during the same period. There were 25 men and 352 women, i e a male:female ratio of 1:14 In the men the mean age was 50 1 (range 17–67) years, and in the women it was 50 4 (11–78) years

Indications for surgical treatment were obstructive or compressive symptoms, continuous growth of solitary or multiple cold nodules; possibility of malignancy, and cosmetic concern or fear of malignancy by the patient.

Enucleation of all the nodules was performed to prevent recurrent nerve and parathyroid injury The localization of epidermal growth factor receptor was studied in 28 adenomatous goitres using immunohistochemical techniques previously reported[5] Sections were stained using the avidin–biotin–peroxidase complex method[6] Antihuman epidermal growth factor receptor monoclonal antibody (Oncor, Gaithersburg, Maryland, USA) was used as the primary antibody

Results

Of the 377 patients, 343 were operated on as a primary procedure, and 34 (9·0 per cent) for nodular recurrence. Among these 34 patients, the number of previous operations was one in 29, two in four, and three in one. The interval between the first and second operation was ⩽10 years in 14 patients, 11–19 years in 13, and ⩾20 years in seven. All had shown multiple bilateral small nodular lesions at the initial operation Nodular lesions detected during the initial operation had been enucleated as far as possible. Patients with recurrence had not received endogenous TSH suppression with thyroid hormone after surgery.

Adenomatous goitre was complicated by thyroid cancer in 18 (4 8 per cent) patients who were all women; only one was under 40 years of age. The cancer was papillary in 17 patients and follicular in one.

Only one of the tumours was symptomatic and had been detected before operation; the remaining 17 were detected coincidentally. All but one of these occult tumours was <1 cm in diameter, and the concomitant adenomatous goitre was invariably of the multinodular type (*Table 1*). Tumours were detected at the initial operation in 13 patients and at the repeat operation in four.

Localization of epidermal growth factor receptor in adenomatous goitre showed a mixed distribution. Epidermal growth factor receptors were expressed in part in apparently benign areas of the adenomatous goitre as well as in the malignant tumours (*Figure 1*). This localization pattern was observed more often in multiple than single nodular lesions in those patients without latent malignancy (*Table 2*). In patients with multinodular adenomatous goitre complicated by cancer, epidermal growth factor receptors were frequently found to be localized not only in the foci of tumours but also in the surrounding adenomatous lesions.

Table 1 *Clinicopathological findings of the 18 patients with adenomatous goitre complicated by thyroid cancer*

Sex ratio (M.F)	0 18
Age	
<40 years	1
⩾40 years	17
Incidence of concomitant thyroid cancer	18* of 377
Histology	
Papillary cancer	17
Follicular cancer	1
Size (diameter)	
<1 cm	17
⩾1 cm	1
Gross findings of adenomatous goitre	Multinodular type in all

*Seventeen of the 18 cases were unsuspected

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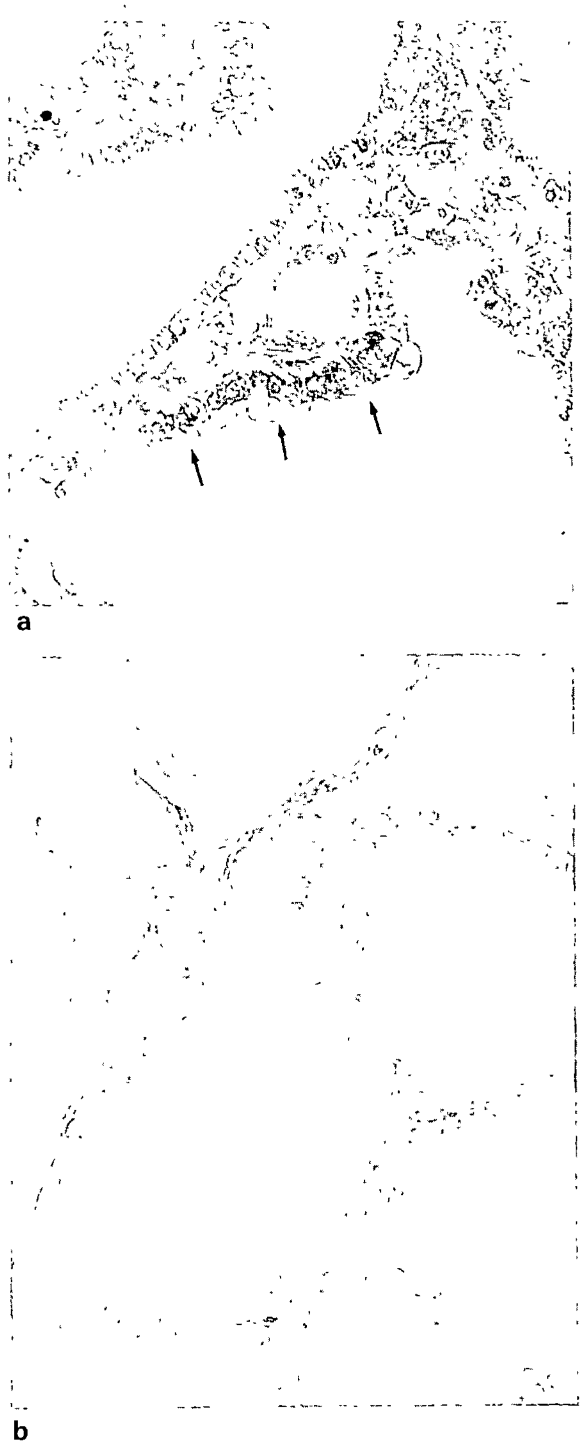

Figure 1 *Expression of epidermal growth factor receptor in adenomatous goitre* **a** *Epidermal growth factor receptors expressed in part (arrowed) in apparently benign areas of the adenomatous goitre* **b** *Negative staining case (Immunohistochemical stain, original magnification ×1200)*

Table 2 *Immunohistochemical staining of epidermal growth factor receptor in adenomatous goitre*

Adenomatous goitre	No of cases	Positive staining
Without latent malignancy		
Multiple type	10	6
Single type	11	2
Complicated with occult cancer	7	
Cancerous lesions		5
Surrounding benign lesions		3

Discussion

Various therapeutic approaches have been suggested for benign nodular lesions of the thyroid[3,4,7]. There is no consensus regarding a specific therapeutic approach

In this study patients treated surgically were reviewed with respect to their clinical and laboratory features to try to establish an appropriate therapeutic strategy.

In the primary operation, the nodules (confirmed macroscopically) were enucleated as far as possible. Some patients had small multicystic nodular lesions. Complete removal of all the nodular lesions by the enucleation method might be difficult although there were no postoperative complications.

Postoperative thyroid hormone suppressive therapy was not provided since in no patient was there an increase in serum TSH after enucleation of the multiple nodules. At the time of the study this medical management was not used in Japan. It is uncertain whether TSH-suppressive treatment would have prevented recurrence in these cases. Anderson *et al*[8] have recently reported that postoperative long-term thyroxine might prevent recurrence of multinodular goitre.

Adenomatous goitre was complicated by cancer in 4·8 per cent of patients, higher than the general incidence of thyroid cancer. Reports from the Third National Cancer Survey[9] suggest that the age-adjusted incidence of clinical thyroid cancer of all ages, races and sexes combined is only 0·004 per cent in the USA. Maruchi *et al.*[10] have reported that the prevalence of thyroid cancer is 1·3 (0·6 for men and 1·9 for women) per 1000 examined according to their population surveys in a non-endemic region of Japan Greenspan[3] noted an overall incidence of malignancy in multinodular goitre of approximately 0·5 per cent. The concomitant cancers were asymptomatic except in one patient. Goitres were of the multinodular type in all these patients; whether these small malignant lesions would have remained occult cannot be determined.

Epidermal growth factor receptor, a well known product of the oncogene *erb*B, is probably involved in carcinogenesis and cell proliferation[11]. The frequent expression of epidermal growth factor receptor in malignancies of the thyroid gland has been demonstrated immunohistochemically[5]. Duh and Clark[12], employing a radioreceptor analysis, reported that human neoplastic thyroid tissue binds more epidermal growth factor than does normal thyroid tissue

The present finding of the frequency of epidermal growth factor receptor expression in adenomatous goitre, which is a benign hyperplastic disease, raises the possibility that the condition might have precancerous potential This tendency was more evident in patients with multinodular lesions, but the significance of this finding in benign hyperplastic tissue is unclear. Long-term follow-up of such cases may resolve the significance of this observation

Clinical and morphological reviews of adenomatous goitre treated surgically in the past 15 years led to the following suggestions concerning therapeutic treatment. Endogenous TSH-suppression therapy with a subtoxic dose of thyroxine (usually 0·1–0·2 mg daily) for 1–2 years should be attempted for non-cystic small nodular lesions consisting of a few discrete nodules <2 cm in size. Surgical treatment should be considered for multinodular lesions occupying one whole lobe or both lobes. Near-total lobectomy leaving the posterior lateral capsule of the involved lobe intact is generally desirable for prevention of recurrence and complications after operation Reeve *et al.*[13] have recommended that total thyroidectomy is the procedure of choice for multinodular goitre where the entire gland is involved. A study of thyroid hormone TSH-suppression therapy after operation should be carried out.

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Plasma fatty acid profiles in benign breast disorders

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Breast pain (mastalgia) and macroscopic breast cysts present commonly. Mastalgia may be improved by dietary manipulation to reduce saturated fat or supplement essential fatty acid intake. Fatty acid profiles were measured in women with mastalgia and breast cysts, before and during treatment with evening primrose oil, a rich source of essential fatty acids. The fatty acid profiles of both groups of patients were abnormal, with increased proportions of saturated fatty acids and reduced proportions of essential fatty acids. Treatment with evening primrose oil improved the fatty acid profiles towards normal, but this was not necessarily associated with a clinical response.

There are marked geographical variations in the incidence of breast cancer, which correlate with the dietary fat intake of these populations[1]. Similar, but less convincing, relationships are found in benign breast disease[2,3]. Intervention to reduce the dietary saturated fat intake improves the symptoms of cyclical breast pain and nodularity[4]. Dietary supplementation with essential fatty acids in the form of evening primrose oil (Efamol; Scotia Pharmaceuticals, Guildford, UK), a rich source of the polyunsaturated *n*-6 essential fatty acid γ-linolenic acid (GLA), also produces an improvement in these symptoms[5,6]. Essential fatty acid supplementation, however, has no effect on macroscopic breast cyst recurrence[7]. Breast pain (mastalgia) and macroscopic breast cysts are the most common benign breast disorders which present to surgeons. When questioned directly 66 per cent of women report breast pain[8] and it has been estimated that about 7 per cent of western women develop macroscopic breast cysts[9]. In this study plasma fatty acid levels were measured in women with severe mastalgia and macroscopic breast cysts, before and during therapy with evening primrose oil, to examine the fatty acid profiles of these women and identify changes with treatment.

Patients and methods

The patients reported here were recruited as part of two previously reported clinical trials[6,7].

Mastalgia trial

Thirty-six women with severe cyclical mastalgia and eight with severe non-cyclical mastalgia were randomized to active or placebo arms of the trial A pretreatment blood sample was collected into an ethylene diamine tetra-acetic acid (EDTA)-coated tube. Those in the active arm of the trial were given eight capsules of evening primrose oil daily (320 mg GLA) for 4 months. Patients in the placebo arm of the trial were given eight capsules containing liquid paraffin daily for 2 months, and were then crossed over to take eight capsules of evening primrose oil daily for the final 2 months of the trial. Clinical response was assessed and blood samples were collected monthly. The method of assessing response has been described elsewhere[10].

Breast cyst trial

Two hundred women with palpable breast cysts requiring aspiration were randomized to take either six capsules of evening primrose oil daily (240 mg GLA) or placebo for 12 months. A pretreatment EDTA blood sample was collected before entry. Patients were reviewed clinically and blood samples collected 4-monthly during the trial. Stored samples were lost on a third of patients because of freezer breakdown, leaving plasma from 145 patients for fatty acid analysis.

Controls

EDTA blood samples were taken from a group of screened, clinically normal, women with no history of breast disease or atopy.

Blood samples and essential fatty acid analysis

The plasma was separated by centrifugation and stored at −20°C. During storage, 20 samples (<3 per cent) oxidized and were not available for analysis. The essential fatty acid assays were performed blind by the Efamol Research Institute, Nova Scotia, by gas chromatography after the lipids had been extracted and the phospholipid fraction separated by thin layer chromatography[11]. The phospholipid fraction was studied because it is relatively resistant to short-term changes in diet. Fatty acid esters are expressed as proportions (milligrams per 100 milligrams) of the total fatty acid esters present in the phospholipid fraction, and were compared using Student's unpaired two-tailed *t* test. For brevity, results for only the esters of the major saturated fatty acids, palmitic and stearic acid, and the esters of the direct precursor and metabolites of GLA are reported. Patients withdrawing from the trials were included in the analyses of change in proportions of fatty acid esters with treatment to the point at which they withdrew, but were not included in the analyses comparing change with response

Results

Mastalgia

Patients with cyclical and non-cyclical mastalgia showed differences from the control population in the proportions (milligrams per 100 milligrams of the total fatty acid esters in the phospholipid fraction) of the fatty acid esters (*Table 1*). In the patients with cyclical mastalgia, the proportions of the esters of the saturated fatty acids, palmitic and stearic acid, were significantly elevated. The proportions of the esters of the polyunsaturated essential fatty acids, linoleic, dihomo-γ-linolenic (DGLA) and arachidonic acid, were significantly

Table 1 *Proportions of plasma fatty acid esters in controls and patients with mastalgia*

	Controls ($n = 32$)	Cyclical mastalgia ($n = 36$)	Non-cyclical mastalgia ($n = 8$)
Essential fatty acid ester (mg/100 mg)			
Linoleic	26·8(3·4)	23·6(3·2)†	25·1(3·7)
Dihomo-γ-linolenic	2·9(0·7)	2·5(0·6)†	2·2(0·9)
Arachidonic	11·1(1·5)	8·3(1·5)†	8·3(2·5)*
Saturated fatty acid ester (mg/100 mg)			
Palmitic	26·7(1·7)	28·9(2·0)†	29·9(4·3)
Stearic	9·1(2·0)	11·0(2·2)†	10·9(2·2)

Values are mean(s.d.). *$P < 0·05$; †$P < 0·01$ (mastalgia *versus* controls, Student's unpaired two-tailed *t* test)

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reduced. The differences in the patients with non-cyclical mastalgia were in the same direction, but only the reduced proportion of arachidonic acid was significant; however, the numbers were small in this group.

There was no significant difference in the proportions of the fatty acid esters between the patients with cyclical and non-cyclical mastalgia. These groups were combined to analyse changes in the proportions of fatty acid esters with treatment. Data obtained before treatment and at 2 months include the patients treated with evening primrose oil after initial placebo treatment. Evening primrose oil produced a significant increase in the proportion of DGLA, the metabolite of GLA, after 2 and 4 months of treatment. There were no changes in the proportions of the esters of the saturated fatty acids (*Table 2*). There were no significant changes in the proportions of fatty acid esters after 2 months' treatment with placebo (*Table 2*).

Patients were divided on the basis of clinical response to treatment with evening primrose oil. Those who obtained a useful response had a significantly lower proportion of DGLA before treatment. After 4 months' treatment there was no difference in this proportion between the response groups (*Table 3*)

Table 2 *Changes in proportions of plasma fatty acid esters in patients with mastalgia after treatment*

	Before	2 Months' treatment	4 Months' treatment
Evening primrose oil-treated group			
No. of patients	43	41	18
Essential fatty acid ester (mg/100 mg)			
Linoleic	24·1(3·3)	24·6(3·3)	24·2(3·2)
Dihomo-γ-linolenic	2·5(0·5)	3·0(0·6)*	3·1(0·7)*
Arachidonic	8·5(1·6)	8·8(1·6)	9·4(2·5)
Saturated fatty acid ester (mg/100 mg)			
Palmitic	28·9(1·9)	29·1(1·9)	28·5(1·7)
Stearic	10·9(2·2)	10·8(2·6)	11·1(2·8)
Placebo-treated group			
No. of patients	19	20	
Essential fatty acid ester (mg/100 mg)			
Linoleic	24·1(3·7)	24·1(3·5)	
Dihomo-γ-linolenic	2·3(0·9)	2·7(0·6)	
Arachidonic	8·1(1·6)	8·7(1·6)	
Saturated fatty acid ester (mg/100 mg)			
Palmitic	28·9(3·3)	28·5(1·7)	
Stearic	10·7(2·3)	11·0(2·3)	

Values are mean(s.d.) $*P < 0{\cdot}01$ (treatment *versus* pretreatment, Student's unpaired two-tailed t test)

Table 3 *Relationship between proportions of plasma fatty acid esters in patients with mastalgia and response to treatment*

	Before	2 Months' treatment	4 Months' treatment
Useful response to evening primrose oil			
No. of patients	17	16	9
Essential fatty acid ester (mg/100 mg)			
Linoleic	23·7(3·9)	24·6(3·5)	24·8(2·9)
Dihomo-γ-linolenic	2·2(0·7)‡	2·8(0·6)†	3·1(0·6)†
Arachidonic	8·5(1·7)	9·1(1·4)	10·0(2·7)
Saturated fatty acid ester (mg/100 mg)			
Palmitic	30·0(3·0)	29·3(2·3)	28·5(1·5)
Stearic	11·2(2·5)	11·1(3·1)	11·4(2·7)
Poor response to evening primrose oil			
No. of patients	21	22	9
Essential fatty acid ester (mg/100 mg)			
Linoleic	23·6(2·4)	24·1(2·9)	23·6(3·5)
Dihomo-γ-linolenic	2·8(0·6)	3·1(0·5)*	3·0(0·9)
Arachidonic	8·1(1·6)	8·7(1·8)	8·7(2·3)
Saturated fatty acid ester (mg/100 mg)			
Palmitic	28·9(2·1)	29·0(1·7)	28·4(2·0)
Stearic	10·5(2·0)	10·8(2·1)	10·8(3·0)

Values are mean(s.d.) $*P < 0{\cdot}05$; $\dagger P < 0{\cdot}01$ (treatment *versus* pretreatment), $\ddagger P < 0{\cdot}05$ (useful *versus* poor response), all comparisons, Student's unpaired two-tailed t test

Table 4 *Proportions of plasma fatty acid esters in patients with breast cysts and changes after treatment*

	Before	4 Months' treatment	8 Months' treatment	12 Months' treatment	4 Months after treatment
Evening primrose oil-treated group					
No of patients	75	64	64	59	61
Essential fatty acid ester (mg/100 mg)					
Linoleic	24·2(4·8)§	25·0(4·7)	25·4(4·9)	24·4(4·8)	25·6(4·4)
Dihomo-γ-linolenic	2·5(1·1)‡	3·0(0·9)†	3·0(1·2)*	3·3(1·1)†	2·6(1·1)
Arachidonic	8·0(1·6)§	8·5(2·0)	8·7(2·7)	9·3(2·1)†	9·6(2·3)†
Saturated fatty acid ester (mg/100 mg)					
Palmitic	29·3(2·9)§	29·0(3·1)	28·3(3·8)	28·2(3·1)*	28·0(3·0)†
Stearic	11·4(2·7)§	11·0(2·0)	10·9(2·8)	11·2(2·4)	10·7(3·2)
Placebo-treated group					
No. of patients	70	60	57	57	57
Essential fatty acid ester (mg/100 mg)					
Linoleic	24·9(4·3)‡	24·8(4·2)	25·1(4·8)	25·7(4·5)	25·4(5·0)
Dihomo-γ-linolenic	2·3(0·6)§	2·3(0·8)	2·5(0·6)	2·4(0·7)	2·7(1·0)*
Arachidonic	8·4(2·1)§	8·9(2·6)	9·1(2·2)	9·6(2·2)†	9·6(2·0)†
Saturated fatty acid ester (mg/100 mg)					
Palmitic	29·7(2·1)§	29·8(2·1)	28·8(1·9)*	28·5(2·1)†	27·6(2·6)†
Stearic	10·6(3·2)§	10·6(3·0)	10·6(3·5)	10·1(2·5)	10·7(2·7)

Values are mean(s.d.). $*P < 0{\cdot}05$; $\dagger P < 0{\cdot}01$ (treatment *versus* pretreatment); $\ddagger P < 0{\cdot}05$, $\S P < 0{\cdot}01$ (patients with cysts *versus* controls), all comparisons, Student's unpaired two-tailed t test. For controls see *Table 1*

Cysts

There were no significant differences in the pretreatment proportions of fatty acid esters between the patients with breast cysts randomized to receive evening primrose oil or placebo, but both groups showed significant differences from the control population (*Table 4*).

Treatment with evening primrose oil produced an immediate significant increase in the proportion of DGLA, which returned to the pretreatment proportion 4 months after completing treatment. There was a gradual increase in the proportion of arachidonic acid, which became significant after 12 months and was maintained 4 months after completing treatment. The proportion of the saturated fatty acid palmitic acid fell gradually, the difference becoming significant at 12 months (*Table 4*) Treatment with placebo led to similar changes in arachidonic and palmitic acid to those seen in the group treated with evening primrose oil, but no change in DGLA during treatment

There was no relationship between the proportions of the fatty acid esters before or after treatment and cyst recurrence, whether the patient was treated with evening primrose oil or placebo

Discussion

These studies demonstrate that patients with severe mastalgia (cyclical and non-cyclical) and macroscopic breast cysts have similar and abnormal fatty acid profiles. The abnormal profiles are of reduced proportions of the esters of the polyunsaturated essential fatty acid metabolites of linoleic acid, and increased proportions of the esters of the saturated fatty acids palmitic and stearic acid. These abnormalities produce a marked elevation of the saturated.unsaturated fatty acid ratio when compared with the control population.

The underlying causes of severe mastalgia and breast cysts are not known, but both display features suggesting a hypersensitivity of the breast epithelium to circulating female hormones. Cyclical mastalgia is an exaggeration of normal premenstrual breast pain and may be treated successfully with danazol and bromocriptine[10] Breast cysts present more commonly during the luteal phase of the menstrual cycle and become very uncommon after the menopause[9] Their recurrence may be reduced by treatment with danazol[12]. A cellular environment with a higher ratio of saturated to unsaturated fatty acids leads to an endocrinologically hypersensitive state, due to increased potency of steroid hormones esterified to saturated fatty acids and higher receptor affinity in such an environment. Low · levels of DGLA, via its metabolite prostaglandin E_1, may also affect the peripheral actions of prolactin[13]

The metabolic pathway of the *n*-6 essential fatty acids is by alternate desaturation and elongation steps. The elongations occur rapidly, with the desaturations being rate limiting. The δ-6-desaturation step between linoleic and GLA is severely rate limiting, and is inhibited by high levels of saturated fats. Administration of essential fatty acids in the form of evening primrose oil, which is rich in GLA, bypasses this step. GLA is measurable in only trace amounts as it is rapidly metabolized to the more stable metabolite DGLA, the proportion of which is immediately raised by evening primrose oil treatment There was a gradual reduction in the proportions of the saturated fatty acids, which became significant after 12 months and remained so 4 months after completing treatment This was also seen in the patients treated with placebo, which suggests that it was related to long-term changes towards a diet lower in saturated fats. The reason for the gradual increase in the proportions of arachidonic acid in patients with breast cysts treated with placebo, and of DGLA 4 months after completing placebo treatment, is not known.

Patients with mastalgia and breast cysts had abnormal fatty acid profiles before treatment Evening primrose oil significantly improved the symptoms of pain and nodularity[6], but no effect was observed on breast cyst recurrence[7] despite improvements in the fatty acid profile. Patients with mastalgia who obtained a clinically useful response to evening primrose oil had a pretreatment proportion of DGLA that was significantly lower than that of patients who obtained a poor response. As the proportion of DGLA was similar after 4 months' treatment, the increase was greater in those who obtained a clinically useful response Whether this is significant in terms of the response is not clear. There was no relationship between breast cyst recurrence and the proportions of the fatty acid esters, before or after treatment with evening primrose oil or placebo. The therapeutic failure of evening primrose oil in patients with breast cysts was not due to a subgroup of patients with a marked essential fatty acid deficiency which treatment was not able to restore.

Similar abnormalities have been identified in the fatty acid profiles of patients with cyclical and non-cyclical mastalgia, and breast cysts. The different clinical pictures and lack of association between proportions of fatty acid esters and breast cyst recurrence suggest a multifactorial aetiology This may include excess release of prolactin[14,15] and the stage of breast development or involution at which these factors exert their influence[16].

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Comparison of Nissen total and Lind partial transabdominal fundoplication in the treatment of gastro-oesophageal reflux

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Fifty-two patients with gastro-oesophageal reflux disease refractory to medical treatment were randomized to undergo a Nissen total (360° wrap) or Lind partial (300° wrap) transabdominal fundoplication. Each group was comparable in number (26 patients), mean age (47 and 48 years) and sex distribution (eight women). Preoperative and postoperative assessment involved a modified Visick score, 22-h intraoesophageal pH monitoring, endoscopy and manometry. Follow-up was at 6 weeks and between 3 and 33 (mean 13) months. The prevalence of heartburn and regurgitation and the results of pH monitoring improved significantly after both operations ($P < 0{\cdot}001$). At early assessment eight previously asymptomatic patients (31 per cent) from the Nissen group and six (23 per cent) from the Lind group experienced difficulty swallowing. Ten patients (38 per cent) in each group complained of 'gas bloat'. Both complications had improved at late assessment in the majority of patients. No statistically significant advantage could be demonstrated for either operation.

Antireflux surgery is an effective treatment option for the majority of patients with chronic disabling gastro-oesophageal reflux[1]. Improvements are required in four areas: (1) to reduce the 15 per cent of patients reported to have continuing symptoms after fundoplication[2]; (2) to improve durability – the number of patients with abnormal pH results increases with the length of time after surgery[3]; (3) to reduce the frequency of postoperative complications – transient dysphagia occurs in up to 100 per cent and the 'gas bloat' syndrome in 38 per cent of patients after a Nissen fundoplication[4]; and (4) to minimize the invasive nature of this type of surgery by employing endoscopic or laparoscopic techniques[5,6].

This study examines the first three areas and whether postoperative complications are less frequent after partial or total fundoplication while reflux control is maintained[7]. The results of two transabdominal antireflux procedures, the 'floppy' Nissen total fundoplication (360° wrap)[8] and the Lind partial fundoplication (300° wrap)[9] were compared.

Patients and methods

Patients

The study population comprised 52 consecutive patients with reflux symptoms and abnormal acid reflux on intraoesophageal pH monitoring refractory to at least 1 year of supervised medical treatment Patients were randomized to undergo a Nissen total or Lind partial fundoplication Each group comprised 26 patients (18 men, eight women). The mean age was 47 (range 23–82) years in the Nissen group and 48 (range 26–70) years in the Lind group. Informed consent was obtained from each subject

Surgery

All patients underwent a standardized transabdominal operation through an upper midline incision with similar mobilization of the gastro-oesophageal junction in both operations. Peroperative broad-spectrum antibiotics were administered in each case. Division of the triangular ligament was not routinely performed and the short gastric vessels were divided only when the fundoplication could not otherwise be constructed without it being under tension. Both operations involved tightening the hiatus and the construction of a 3-cm long fundoplication around the intra-abdominal oesophagus using interrupted 2/0 linen sutures The 'floppy' Nissen total fundoplication (360° wrap) was performed using the method of Donahue and Bombeck with a mercury-weighted dilator (40 Fr) positioned across the gastro-oesophageal junction[10]. The Lind operation involved the placement of three rows of sutures The first two rows were placed in the left and right lateral positions and the third row more anteriorly, leaving a 60° bare area on the anterior aspect of the oesophagus The use of a dilator was not necessary in this latter group. An additional suture in both operations anchored the fundus and part of the oesophageal musculature to the undersurface of the diaphragm. All oesophageal strictures were dilated at the time of surgery

Assessment

Preoperative assessment comprised symptomatic grading using a modified Visick symptom score (*Table 1*)[11], intraoesophageal pH monitoring, manometry and fibreoptic endoscopy Early symptomatic assessment was performed 6 weeks after operation Evaluation between 3 and 33 (mean 13) months involved repeat pH monitoring, manometry and endoscopy, with symptomatic assessment and clinical review performed 'blind' by an independent observer Heartburn was defined as a sensation of substernal burning radiating into the neck, which came in waves and was made worse by recumbency Regurgitation was defined as the sensation of bitter or sour fluid in the oropharynx[12].

Table 1 *Symptomatic grading (modified Visick symptom score)*[11]

Heartburn and regurgitation
1 No symptoms
2 Mild symptoms relieved by simple medical treatment
3 Mild/moderate symptoms not completely relieved by medical treatment
4 Regular severe symptoms not relieved by medical treatment

Dysphagia
1 No difficulty in swallowing
2 Occasional difficulty in swallowing solids, usually helped by a drink
3 Frequent 'sticking' of bulky solids and occasionally of softer foods
4 Only able to take liquids, bordering on complete dysphagia

Gas bloat
1 No gas bloat symptoms
2 Mild symptoms not interfering with eating and activity
3. Mild/moderate symptoms occasionally affecting eating and activity
4 Frequent, distressing gas bloat symptoms

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The term 'gas bloat' was used to describe distressing abdominal fullness after meals, sometimes accompanied by abdominal pain and an inability to vomit or belch[4].

pH monitoring

Changes in intraoesophageal pH were measured using a flexible glass pH electrode (MI 506; Microelectrodes, Londonderry, New Hampshire, USA) positioned 5 cm above the manometrically determined upper limit of the gastro-oesophageal high pressure zone and connected to a portable solid state recorder (Multistore 1 5150; Ormed, Welwyn Garden City, UK). A second connection was made to an electrocardiogram-type electrode on the patient's non-dominant upper arm. Calibration of the system was performed[13] using two standard buffer solutions (pH 7·0 and 4·0) at 37°C. Monitoring was performed over 22 h with the patient fully ambulant at home. Drugs known to affect gastro-oesophageal function were withheld for 24 h before and during this study. All subjects were instructed to abstain from smoking, alcohol, and food and drink with a pH <5·0. A timed record of diet, activity and periods when supine was made. An event marker button recorded any reflux symptoms. The data were analysed by computer (pH Analyser 5153, Ormed). Six reflux parameters were calculated (total percentage reflux time, erect percentage reflux time, supine percentage reflux time, total number of reflux episodes, number of reflux episodes >5 min, time for the longest reflux episode)[14]. Each parameter was examined at the standard pH <4·0 level.

Manometry

Oesophageal manometry was performed using a three-channel low compliance water-perfused catheter system (Standard adult R4A S-S-S; Mui Scientific, Mississauga, Canada) comparable to that described by Arndorfer *et al.*[15]. The pressure of the lower oesophageal sphincter was measured using the station pull-through technique[16] and a mean value calculated from all three channels. With the lowermost channel in the sphincter, motility was assessed in the distal oesophagus during the course of ten 'wet' (5 ml water) and ten 'dry' swallows.

Endoscopy

All patients underwent fibreoptic upper gastrointestinal endoscopy (XQ 10, Olympus, Tokyo, Japan) before and at late assessment after surgery. Oesophagitis was graded by the method of Savary and Miller[17].

Statistical analysis

Paired comparisons of median values were performed using the Wilcoxon signed rank test and unpaired comparisons using the Mann–Whitney *U* test.

Results

Heartburn, regurgitation, dysphagia and gas bloat

Before surgery there was no statistically significant difference between the two patient groups in terms of frequency and severity of heartburn, regurgitation or dysphagia. Both operations produced dramatic improvements in heartburn and regurgitation at early assessment ($P < 0{\cdot}001$) which were maintained at late assessment. Neither procedure proved superior to the other ($P > 0{\cdot}05$) (*Figures 1* and *2*)

Eleven patients (42 per cent) from the Nissen group and 13 (50 per cent) from the Lind group complained of dysphagia before surgery (*Figure 3*). This had improved at early postoperative assessment in 11 of 11 patients from the former and in eight of 13 patients (62 per cent) from the latter group.

A further group of patients developed dysphagia after fundoplication (*Figure 3*). Eight (31 per cent) previously asymptomatic patients from the Nissen group complained of dysphagia after surgery (Visick grade 2, four; grade 3, four) and six (23 per cent) patients from the Lind group (Visick grade 2, four; grade 3, two) (Nissen *versus* Lind, *P* not significant). All patients with severe postoperative dysphagia (Visick grade 3) underwent between one and three dilatations. Taking both groups of patients with dysphagia together a significant improvement in swallowing ability was seen between early and late assessment ($P < 0{\cdot}05$). One patient complained of troublesome dysphagia (Visick grade 3) at late assessment after a Nissen fundoplication. Mild dysphagia not requiring treatment (Visick grade 2) continued to be experienced by a

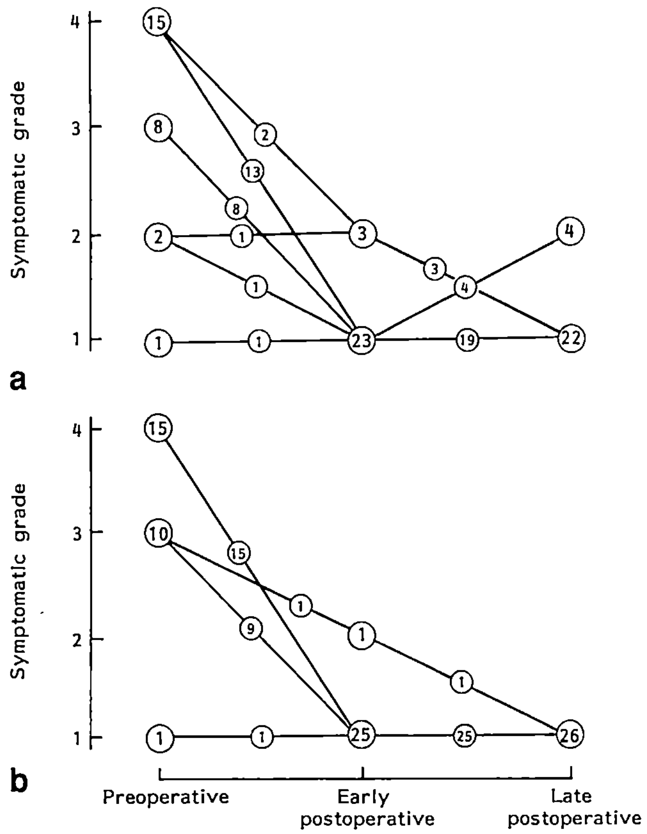

Figure 1 *Heartburn: symptomatic grading before and at early and late assessment after* **a** *Nissen and* **b** *Lind fundoplication* $P < 0{\cdot}001$ (*preoperative* versus *postoperative, Wilcoxon signed rank test*), P *not significant* (*Nissen* versus *Lind, Mann–Whitney* U *test*)

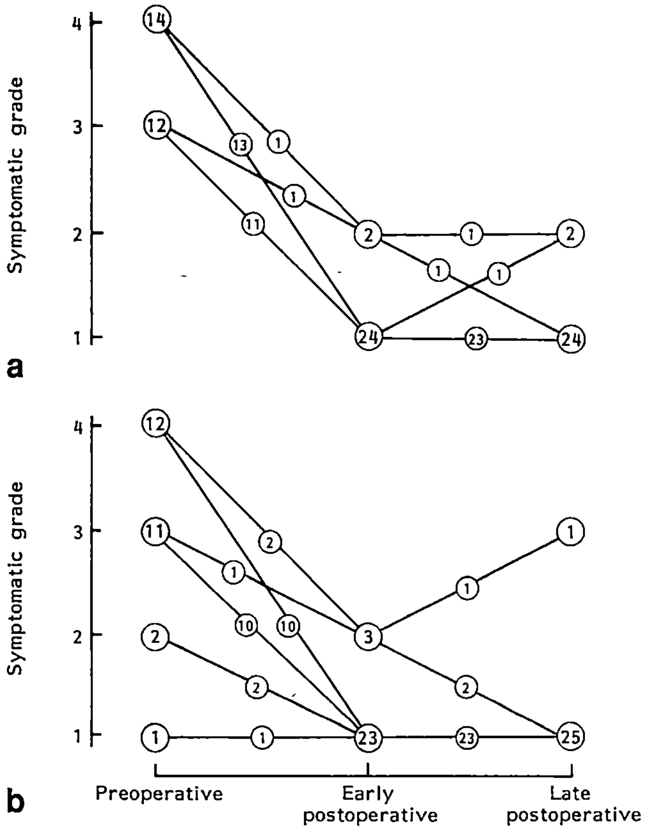

Figure 2 *Regurgitation. symptomatic grading before and at early and late assessment after* **a** *Nissen and* **b** *Lind fundoplication.* $P < 0{\cdot}001$ (*preoperative* versus *postoperative, Wilcoxon signed rank test*); P *not significant* (*Nissen* versus *Lind, Mann–Whitney* U *test*)

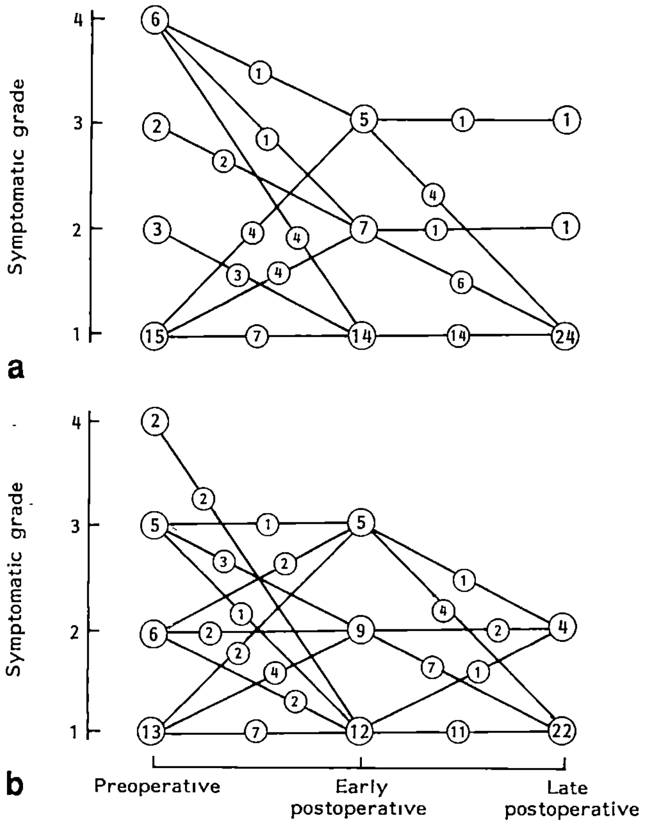

Figure 3 *Dysphagia symptomatic grading before and at early and late assessment after* **a** *Nissen and* **b** *Lind fundoplication*

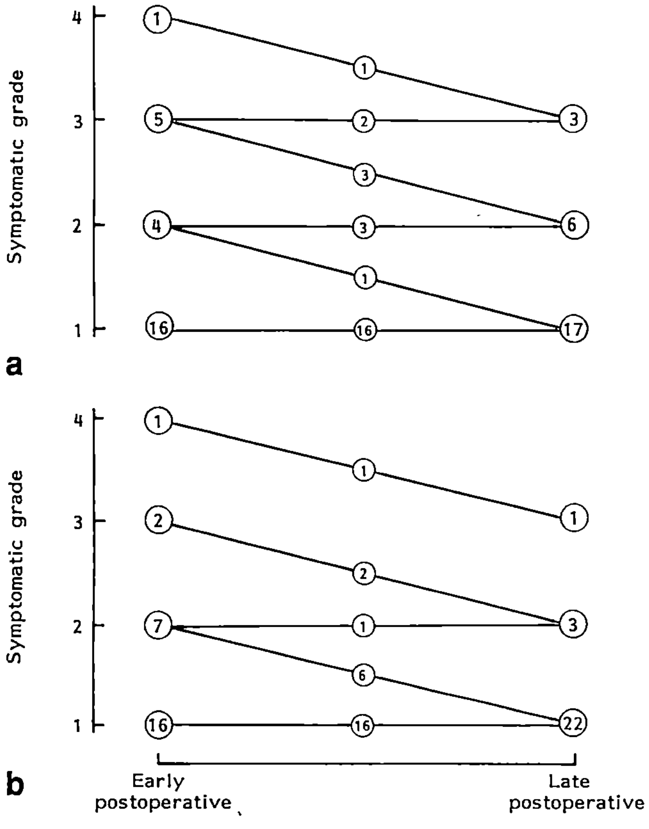

Figure 4 *Gas bloat symptomatic grading at early and late assessment after* **a** *Nissen and* **b** *Lind fundoplication*

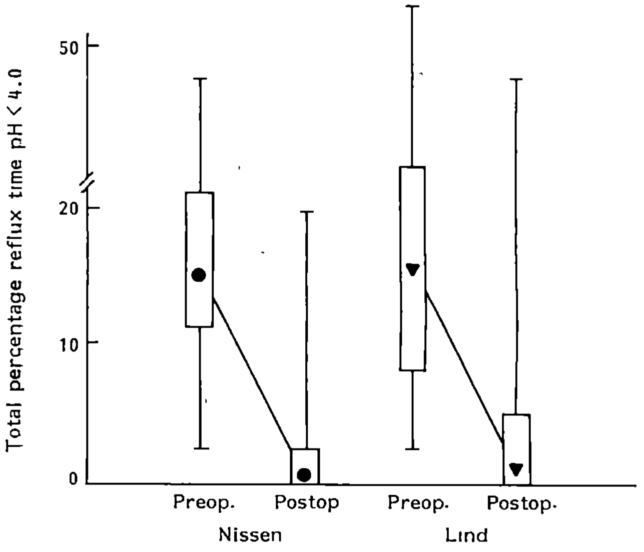

Figure 5 *Total percentage reflux time the results of pH monitoring before and after antireflux surgery Values are median (range, bars, interquartile range, box).* P < *0·001 (preoperative* versus *postoperative, Wilcoxon signed rank test),* P *not significant (Nissen* versus *Lind, Mann–Whitney* U *test)*

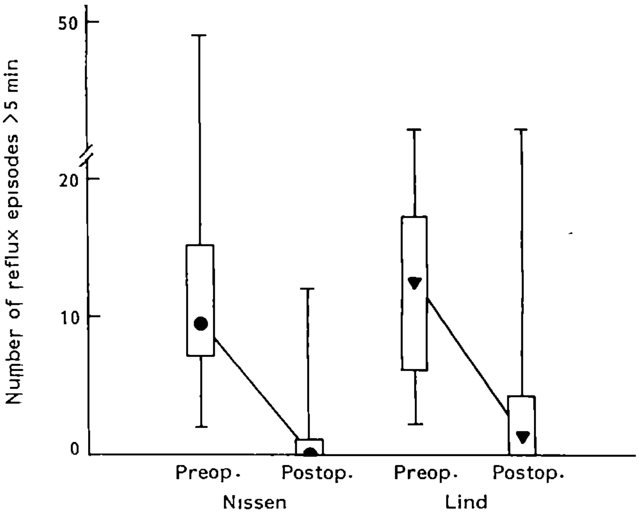

Figure 6 *Number of reflux episodes >5 min; the results of pH monitoring before and after antireflux surgery Values are median (range, bars, interquartile range, box).* P < *0·001 (preoperative* versus *postoperative, Wilcoxon signed rank test);* P *not significant (Nissen* versus *Lind, Mann–Whitney* U *test)*

further patient from the Nissen group and four patients from the Lind group

Gas bloat was reported in ten subjects (38 per cent) from each group at early assessment. This symptom tended to be more troublesome (Visick grade 3 and 4) in patients after a Nissen operation (Nissen, six; Lind, three) (*Figure 4*). A similar trend was maintained at late assessment (Nissen, three; Lind, one) There was a significant improvement ($P < 0·05$) in all grades of gas bloat between early and late assessment in the Lind but not the Nissen group ($P = 0·063$). Gas bloat was more likely to persist at late assessment in patients after a Nissen than a Lind fundoplication.

pH monitoring

All six parameters of pH monitoring significantly improved after both operations ($P < 0·001$). Neither operation produced superior reflux control ($P > 0·05$). *Figures 5* and *6* depict the results before and after surgery for total percentage reflux time at pH < 4·0 and number of reflux episodes > 5 min. These two factors are generally regarded as being of most value in assessing acid reflux[18,19] In this study they are representative of the outcome encountered in all of the six parameters under investigation.

Manometry

Before surgery the median lower oesophageal sphincter pressure was similar in both groups (Nissen 14·8 mmHg, Lind 15·0 mmHg) and was not significantly altered by fundoplication (after Nissen 15·0 mmHg, after Lind 15·0 mmHg). Sphincter relaxation could be demonstrated in all subjects No patient exhibited a manometry tracing during swallowing comparable to that of any of the recognized oesophageal motility disorders[20,21]

Endoscopy

The results of endoscopy were comparable in both groups before and after surgery. Oesophagitis (grades II–III) was present before operation in 11 patients (42 per cent) from the Nissen and nine (35 per cent) from the Lind group, while a Barrett's columnar lined oesophagus was encountered in nine (35 per cent) and 11 (42 per cent) patients respectively. Complete healing of oesophagitis was seen in all patients after fundoplication. Before surgery four patients from the Nissen and three from the Lind group had an oesophageal stricture that required dilatation. All strictures were associated with the presence of columnar mucosa.

Complications

There were no postoperative deaths and splenectomy was not necessary in any patient. All oesophageal function tests were performed without complications. The incidence of wound infection, defined as the presence of pus or a positive wound culture, was two of 26 (8 per cent) for the Nissen group and five of 26 (19 per cent) for the Lind group. One patient developed an incisional hernia after a Lind fundoplication. Six patients (23 per cent) from the Nissen group and nine patients (35 per cent) from the Lind group developed a postoperative chest infection.

Discussion

This investigation demonstrates that transabdominal fundoplication improves reflux symptoms, returns pH values to normal and heals oesophagitis with minimal morbidity and no mortality over a relatively short (mean 13 months) follow-up period.

There were no significant differences between the results of partial and total fundoplication. With the exception of one patient from the Lind group there was no evidence to suggest that either operation was more durable. Whether symptoms continue to be controlled at 5–10 years is speculative[7,22].

Lundell *et al.*[23] reported a mild degree of dysphagia occurring more frequently after a Rossetti fundoplication than a Toupet partial fundoplication (180–200° wrap). This difference had disappeared 3 months later. Postprandial epigastric pain, distension and increased flatulence were experienced more often among those having a total fundoplication The results of the present study tend to support these findings. Dysphagia and gas bloat occurred more often and tended to be worse after the Nissen operation than the Lind. Both symptoms had improved in the majority of patients at late follow-up. The possibility of a Type II error must therefore be considered when interpreting this particular aspect of the trial.

The number of patients with endoscopic oesophagitis or Barrett's mucosa in this study is at variance with that reported by others[23,24]. Heterogeneous patient populations are seen by different oesophageal surgeons[25].

The manometry results are of limited reliance in this study because current techniques have poor reproducibility and a lack of assurance that quantitative pressures are being measured[7]. In the clinical situation Bancewicz *et al.*[26] have shown that detailed manometric studies frequently do not improve clinical management. Manometry was of no value in predicting those patients who were going to develop postoperative dysphagia.

A small group of patients demonstrated symptomatic and endoscopic improvements after operation in spite of having abnormal pH results. In some cases only a small reduction in acid reflux may be required to produce a disproportionate improvement in these parameters. Success may be due to an alteration in the composition of the refluxate not detected by pH monitoring. The majority of patients with significant postoperative acid reflux had a columnar lined oesophagus. It is possible that the underlying pathophysiology in these patients is more complicated and influenced less by fundoplication.

Why a minority of patients were found to have abnormal pH results after a carefully performed standardized operation is unclear. O'Hanrahan *et al.*[27] have shown that recurrent reflux is frequently due to disruption of the fundoplication Presumably technical factors at the time of operation contributed to the early 'failures'. Late recurrence of acid reflux is probably due to a combination of tissue weakening, suture disruption or excessive forces applied to the fundoplication. In this study failure was unrelated to the type of procedure or the individual surgeon performing the operation.

This study shows that, after a carefully performed fundoplication, the majority of patients will have normal oesophageal test results. The requirement for pH monitoring or endoscopy after a standard operation is probably present only in those patients who continue to complain of symptoms or who are found to have reflux complications. Not all patients who complain of heartburn and regurgitation after surgery have abnormal pH results or evidence of oesophagitis and, conversely, not all patients who have abnormal findings have reflux symptoms.

Different transabdominal partial fundoplications have been described for the treatment of gastro-oesophageal reflux[23,28,29] The Lind operation is a typical example but a clear advantage over the 'floppy' Nissen total fundoplication is not demonstrated.

Acknowledgements

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Attitudes of cardiothoracic surgeons in the UK to human immunodeficiency virus

A survey was carried out into attitudes of cardiothoracic surgeons in the UK to human immunodeficiency virus type 1 (HIV-1) infection associated with clinical situations that would normally have been managed surgically with low operative mortality rates and long median survival times. The survey response rate was 72·4 per cent. In patients with acute valvular insufficiency or with continuing angina despite maximal medical therapy (unstable angina) who were HIV-1 antibody positive, 75·8 and 80·8 per cent, respectively, of surgeons would operate. If the patient had end-stage infection, acquired immune deficiency syndrome (AIDS), 29·7 per cent and 34·7 per cent, respectively, would consider surgical intervention. When asked to perform simple procedures such as open lung biopsy or pleurectomy on a patient with AIDS, more than half of surgeons would operate (52·2 and 65·6 per cent respectively). In patients with operable carcinoma of the lung and asymptomatic HIV-1 infection 52·3 per cent would operate. This fell to 15·0 per cent if the patient had a diagnosis of AIDS. The majority of surgeons (77·2 per cent) felt patients should have an HIV-1 antibody test before operation and this rose to 95·6 per cent if patients were in a high-risk group; 60·2 per cent of surgeons had changed their surgical practice to reduce the risks of blood-borne infection.

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The prevalence of human immunodeficiency virus type 1 (HIV-1) infection continues to rise in homosexuals, heterosexuals and children, worldwide. Its commonest mode of transmission is sexual. It can be transmitted by parenteral and mucocutaneous routes[1] The overall prevalence of HIV-1 infection in a large prospective study of San Francisco healthcare workers ($n = 1962$) after exposure to blood from patients infected with HIV-1 was 0·32 per cent[2]; 60 per cent were due to needlestick injuries and 25 per cent followed blood splashes[2]. To date the Center for Disease Control (CDC), Atlanta has reported 37 cases of seroconversion in healthcare workers[3], with a further 23 presently under investigation[2] Rigorous scrutiny by the CDC of all such cases has led some to suggest that the number is likely to be greater than this by at least a factor of ten[4].

Glove perforation occurs in about 20 per cent of surgical procedures[5] and a penetrating injury in 5·6 per cent of cases[6]. A general surgeon in the USA receives on average five needlestick injuries a year[2]. The risk of parenteral exposure increases with operations lasting more than 3 h and if the blood loss[7] exceeds 300 ml. The majority of these exposures were due to deviations from established safety guidelines (CDC. Universal Blood and Body Fluid Precautions)[2]. The exposure of theatre staff to blood is considerable in cardiothoracic surgery. Operations routinely last for more than 3 h, placing the surgeon at significant risk from parenteral and/or mucocutaneous inoculation with blood. Many cardiothoracic surgeons in the USA have called for a review of the strategies of all clinical practices associated with the care of patients undergoing cardiac and thoracic surgery[8]. The Royal Colleges of Surgeons of England and Edinburgh have recently published guidelines relating to HIV-1 infection[9,10] and the surgical patient.

This survey was performed to assess the attitudes of cardiothoracic surgeons in the UK to HIV-1 infection and surgical practice.

Methods

The questionnaire (*Table 1*) was based on that used by Condit and Frater[8] but expanded to include clinical situations that might confront the thoracic surgeon The mailing list for UK surgeons was compiled from the 1989 Hospital Directory of all consultant cardiac and thoracic surgeons and the membership list of the Society of Thoracic and Cardiovascular Surgeons of Great Britain and Ireland. Those known to be performing only paediatric surgery were excluded. Each consultant was sent two extra questionnaires for career trainees in their department. The questionnaire was anonymous and it was impossible to detect non-responders. Follow-up questionnaires were not sent. Respondents understood that the data received, and the comments and opinions, would be analysed and published

Statistical analysis of data was, in the main, not warranted but when performed was by means of the χ^2 test.

Results

There are 135 consultants, 29 senior registrars and 35 career registrars performing cardiothoracic surgery in adults in the UK. Replies were received from 108 (80·0 per cent) of the consultants, 17 of the senior registrars and 16 of the career registrars. Three respondents did not give their grade. There were 144 in total (72·4 per cent). Eighty-seven were cardiothoracic surgeons (60·4 per cent), 29 performed only cardiac surgery (20 1 per cent) and 25 thoracic surgery only (17·4 per cent).

The questions on cardiac patients were not answered by thoracic surgeons and this group was excluded from the analysis of these questions. The thoracic questions were answered by all groups of surgeons but the non-responders (10 per cent) in this section were all cardiac surgeons and they were excluded from the analysis of this section.

There were a small number of 'don't knows' ($n = 1–4$) which were grouped with the affirmative replies. By not giving a definite response it was assumed they did not wish to take the unusual course of refusing a patient surgery.

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Table 1 *Questionnaire and response rates*

Clinical scenario	Affirmative response rate		
	All	Consultants	Juniors
03: A patient with endocarditis and valvular insufficiency needs an urgent valve replacement The patient is HIV positive (i e no AIDS or AIDS-related complex) Will you operate?	91 of 120 (75·8)	65 of 87 (75)	26 of 33 (79)
04 A patient with a left main stem, unstable angina The patient is HIV positive from a previous blood transfusion (no AIDS or related complex) Will you operate?	97 of 120 (80·8)	69 of 87 (79)	28 of 33 (85)
05: A patient with endocarditis and valvular insufficiency needs an urgent valve replacement The patient is HIV positive with AIDS. Will you operate?	35 of 118 (29·7)	29 of 86 (34)	6 of 32 (19)
06 A patient with a left main stem, unstable angina. The patient is HIV positive with AIDS from a previous blood transfusion Will you operate?	41 of 118 (34·7)	32 of 86 (37)	9 of 32 (28)
07: A physician refers you a patient with diffuse pulmonary infiltrate The differential diagnosis includes infection (*Pneumocystis carinii* pneumonia, atypical tuberculosis) or Kaposi's sarcoma The patient is HIV positive with AIDS The request is for an open lung biopsy Will you operate?	74 of 134 (55·2)	57 of 101 (56·4)	17 of 33 (52)
08. A patient who is HIV positive with AIDS has a significant pneumothorax which has not responded to 2 weeks of intercostal drainage. A surgical pleurodesis/pleurectomy is requested. Will you operate?	86 of 131 (65·6)	65 of 98 (66)	21 of 33 (64)
09. A patient with a proven carcinoma of the lung is referred to you for surgery. The patient is HIV positive (no AIDS or related complex) Will you operate?	67 of 128 (52·3)	52 of 97 (54)	15 of 31 (48)
10· A patient with a proven carcinoma of the lung is referred to you for surgery. The patient is HIV positive with AIDS Will you operate?	19 of 127 (15·0)	15 of 95 (16)	4 of 32 (12)
11. Should every patient coming for cardiothoracic surgery be tested for HIV?	105 of 136 (77·2)	81 of 104 (77·9)	24 of 32 (75)
12 Would you wish to see every patient coming for cardiothoracic surgery who is at high risk of HIV infection tested for the virus?	130 of 136 (95·6)	98 of 103 (95·1)	32 of 33 (97)
13: Is there any evidence of a difference in the results after cardiothoracic surgery in patients who are HIV positive compared with a patient who is HIV negative?*	21 of 144 (14·6)		
14. Have you modified your surgical practice in an attempt to reduce exposure to HIV-infected blood? If so how?	77 of 128 (60·2)	51 of 96 (53)	26 of 32 (81)

Values in parentheses are percentages HIV, human immunodeficiency virus, AIDS, acquired immune deficiency syndrome *See text

Clinical situations

Cardiac. The responses to questions 3 and 4 were similar: 75·8 and 80·8 per cent, respectively, of surgeons would offer surgery to an HIV-1 antibody-positive patient When dealing with a patient with acquired immune deficiency syndrome (AIDS) (questions 5 and 6) the response pattern was reversed, with 29·7 and 34·7 per cent, respectively, of the surgeons operating (*Table 1*).

Thoracic When asked to perform an open lung biopsy on a patient with AIDS (question 7) the results were equivocal (55·2 *versus* 44·8 per cent). Surgical pleurectomy or pleurodesis on a patient with AIDS (question 8) would be performed by 65·6 per cent of the surgeons. Opinion was equally divided as to whether surgery for carcinoma of the lung should be performed in an HIV-1 antibody-positive patient Almost all surgeons felt that surgical resection for carcinoma of the lung in a patient with AIDS was inappropriate (*Table 1*). The attitudes of the consultants to these clinical situations were not significantly different from those expressed by junior surgeons.

Preoperative testing. One hundred and thirty-six surgeons gave a definite response to both questions (nos 11 and 12); 77·2 per cent of the surgeons felt that all patients should be tested and 95·6 per cent wished all high-risk patients to be tested. Four consultants volunteered that they were already routinely testing for HIV-1 antibodies in their patients. Again no significant difference was found between consultants and juniors (*Table 1*).

HIV-1 infection and surgical practice Only 14·6 per cent felt that the presence of the HIV-1 virus had a detrimental effect on the surgical outcome, 37·5 per cent felt it had no effect, 37·5 per cent did not know and 10·4 per cent did not respond About 60 per cent of surgeons had already modified their surgical practice in an attempt to reduce exposure to HIV-1 infected blood and other body fluids (no response from 11·1 per cent). Only 53 per cent of consultants had modified their practice whereas 81 per cent of juniors had; this difference was not significant (*Table 1*)

Discussion

The high response rate, 80·0 per cent for consultants and 72·4 per cent overall, was good for a single 'mailshot', and was higher than in three recent surveys (53–67 per cent) of surgical practice and HIV-1 infection[8,11,12].

The clinical situations presented in the questionnaire would normally be managed surgically, with a low operative mortality rate and a median survival time measured in years. The reasons for refusing surgery are probably twofold

First is a belief that the prognosis of HIV-1 antibody-positive patients is so poor that surgery is futile. Current figures[13] show that it could be as long as 10 years before HIV-1 antibody-positive patients develop end-stage disease (AIDS) and possibly a further 2 years before they succumb. There is no reason, therefore, to deny cardiothoracic surgery to an HIV-1 antibody-positive patient. The median survival time for a patient with AIDS who develops Kaposi's sarcoma is greater than 4 years, although for a patient who develops primary cerebral lymphoma it is considerably shorter[14] There will be patients with AIDS in whom surgery is inappropriate but there is no evidence to suggest it is contraindicated. The possibility that the known additional immunosuppressive effect of cardiac surgery[15] could worsen the patient's prognosis could have influenced the surgeons' decision to operate. This may be the case for some HIV-1 infected patients with endocarditis[16].

The second reason is a refusal to put themselves and their staff at risk of being 'exposed' to a uniformly fatal virus. In San Francisco, where 10 per cent of accident and emergency patients are HIV-1 antibody positive, it is estimated[7] that, using current clinical practices, a member of the surgical staff will be infected from an accidental inoculation with body fluids contaminated with HIV-1 every 8 years. These calculations are based on the incidence of needlestick injuries, the seroconversion rate of HIV-1 inoculation injuries, and HIV-1 prevalence rates The parenteral case–exposure rate in general surgery is reported as between 1·7 per cent[7] and 5·6 per cent[6]. A recent American study reported a rate of 20 per cent during cardiac surgery[17]. The seroconversion rate is estimated to be 0·3 per cent[2].

The majority of surgeons wish to know the HIV-1 status of 'high-risk' patients but the identification of such patients is difficult[18]. Recent work has shown HIV-1 seroprevalence rates of between 0·1 and 7·8 per cent in patients with no clinical history suggesting they were at risk of HIV-1 infection. This may explain the wish of over three-quarters (77·2 per cent) of the surgeons to test all patients coming to surgery. A patient may have been recently infected, during which time the routine antibody test remains negative but the patient is both infected and infectious. This seroconversion window[19] is approximately 3 months but may be as long as 3 years. The use of antigen testing (p24 and RT)[20] could reduce the number of patients in this seroconversion window but cannot remove the uncertainty that it produces. The screening of patients implies that knowledge of a patient's serological status will reduce the risk of parenteral exposure but knowledge of a patient's HIV-1 status does not reduce the frequency of accidental exposure to blood and body fluids[7,21]. Many of the surgeons surveyed argued that to treat all patients as positive ('universal precautions') would be time-consuming, impractical, expensive and would affect patient turnover. A recent estimate is that to follow such a course would require a doubling of available theatre time[22] With the advent of HIV-1 infection and other blood-borne retroviral diseases, the adoption of universal precautions in all cases is probably the best way to address this problem

Despite adherence to the principles of universal precautions, certain invasive surgical and dental procedures have been implicated in the transmission of hepatitis B virus from infected surgeons to patients. Such procedures include cardiothoracic, colorectal and obstetric/gynaecological surgery, and are defined by the CDC as 'exposure prone'. The risk of transmission of HIV-1 from surgeon to patient is unknown. Experience with the hepatitis B virus, which is considerably more infectious than HIV-1, suggests that the risk of transmission of HIV-1 during procedures that are not exposure prone is minimal[23]. The CDC recommends that those surgeons who perform exposure-prone procedures should know their hepatitis B surface antigen and HIV-1 antibody status. Mandatory HIV-1 testing of all surgeons or those performing exposure-prone procedures is not recommended[23]. Such testing, however, may make it easier for those who become positive for HIV-1 during the course of their work to claim compensation.

There are areas of current cardiothoracic practice that need alteration if the exposure to potentially contaminated body fluids is to be reduced. Protective glasses and a mask should be worn when performing endoscopic procedures and many surgeons stated that they had altered their practice accordingly. The use of the oscillating saw during sternotomy produces a blood and bone aerosol that can penetrate conventional surgical masks[24] The nature of the aerosol may differ with the type of saw and some surgeons have changed instruments for this reason. Double gloving has been shown to reduce cutaneous exposure to blood and body fluids by 60 per cent[7], and their use should be considered by all theatre staff. Surgeons should abandon the use of hand-held needles, and instruments should no longer be passed directly from scrub nurse to surgeon; an intermediate mat or dish should be used. There is proven benefit to the surgeon in following this course; San Francisco General Hospital has the lowest reported parenteral exposure rate (1·8 per cent)[7].

In areas of high prevalence the establishment of protocols for prophylactic zidovudine therapy after accidental exposure should be considered[25].

This survey demonstrates a real concern amongst cardiothoracic surgeons about HIV-1 infection but refusing to operate on such patients and testing for HIV-1 status alone is not the way to resolve this problem. Changes in operative practice and the institution of universal precautions may minimize the risk of HIV-1 infection in the healthcare worker. This will take time and considerable resources are needed to protect those at the 'sharp end' of clinical practice.

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Announcement

The International Association for the Surgery of Trauma and Surgical Intensive Care (IATSIC) was founded in Toronto in 1989 during International Surgical Week. It is an affiliated association of the International Surgical Society.

The Society has become an immediate success and was responsible for five main sessions on trauma and intensive care at the Stockholm meeting last year. A British chapter has been formed with Professor Brian Rowlands (Belfast) as Chairman and Mr Alberic Fiennes (St George's, London) as Secretary. Any surgeon interested in joining this new Association should contact the Secretary at the following address. Mr Alberic G. T. W. Fiennes, Senior Lecturer, Department of Surgery, St George's Hospital Medical School, Jenner Wing, Cranmer Terrace, London SW17 0RE, UK.

Miles Irving

Br. J. Surg. 1992, Vol. 79, May, 419–420

Laparoscopic contact hepatic ultrasonography

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Lack of tactile sensation at laparoscopy may limit the surgeon's ability adequately to explore and evaluate visualized structures. Contact ultrasonography is a sensitive and specific means of exploring the biliary tree, pancreas and liver that is superior to transabdominal ultrasonography in the detection of hepatic and pancreatic neoplasms[1,2]. A technique has been developed which allows currently available ultrasonographic probes to be introduced into the abdominal cavity via a large-bore laparoscope cannula (*Figure 1*) to perform contact ultrasonography without laparotomy.

Surgical technique

Seven patients presenting with primary and secondary hepatic malignancy underwent preoperative staging of disease by chest radiography, hepatic ultrasonography, unenhanced and iodized oil emulsion enhanced computed tomography of the liver, and hepatic angiography. Under general anaesthesia and immediately before intended laparotomy for hepatic resection, each patient underwent diagnostic laparoscopy and laparoscopic ultrasonography. Insufflation of the peritoneal cavity was performed in the usual manner and initial laparoscopy undertaken through the umbilical cannula. The laparoscope was transferred from the umbilical to an epigastric cannula and a guide rod introduced via the umbilical trocar (Endopath T1011; Ethicon, Edinburgh, UK) which was removed. A dilator (20 mm in diameter) with large-port assembly (Oxylitre, Edinburgh, UK) (*Figure 1*) was railroaded over the guide rod under direct vision. The rod and dilator were removed and a 5- or 7·5-MHz ultrasonographic probe (Aloka; Keymed, Southend-on-Sea, UK) was introduced via the large cannula (*Figure 2*) and was left in place until the end of the operation. A reduction sleeve could be employed if smaller instruments are to be passsed via the large cannula. The dilator and reduction sleeve lock on to the large cannula to prevent loss of pneumoperitoneum. The probe was directed over both lobes of the liver, the gallbladder, the extrahepatic biliary tree and the pancreas.

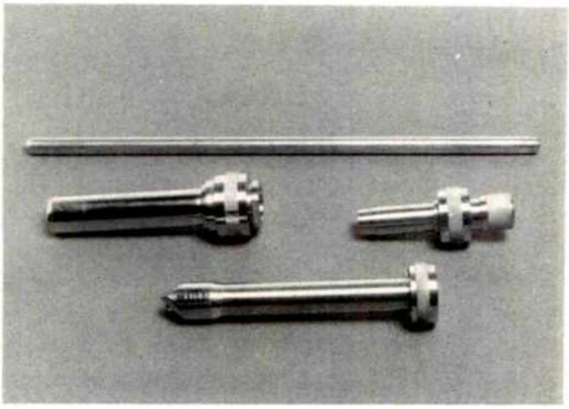

Figure 1 *Guide rod, large cannula, reduction sleeve and dilator/introducer*

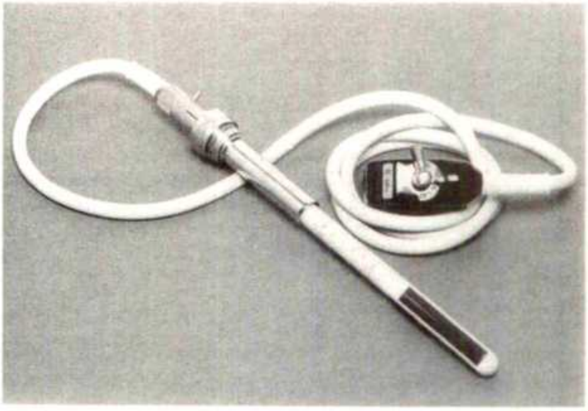

Figure 2 *The 5-MHz rectal ultrasonographic probe passed through the large cannula*

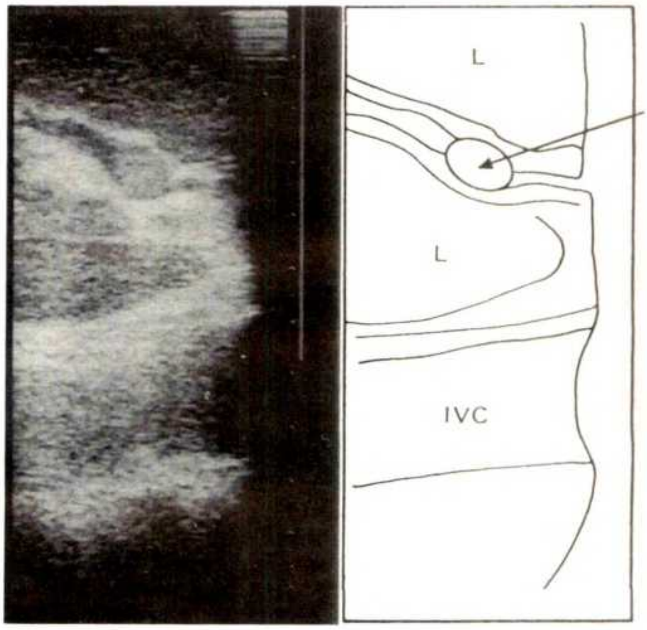

Figure 3 *Laparoscopic ultrasonogram of tumour thrombus (arrowed) in the left portal vein branch. L, liver; IVC, inferior vena cava*

Results

In two of the seven patients widespread extrahepatic disease was seen at laparoscopy associated with unexpected bilobar metastases on laparoscopic ultrasonography. In one of the remaining five patients, laparoscopic ultrasonography confirmed bilobar metastases, but these were less widespread than had been suspected from preoperative investigations. It confirmed a right-sided hepatoma with unexpected extension of tumour thrombus into the left portal vein (*Figure 3*) in a second patient and revealed unexpected extensive bilateral disease as the only positive finding in a further two. The presence of a solitary resectable metastasis was confirmed in the remaining patient.

Discussion

Preoperative staging of hepatic malignancy with conventional scanning techniques may be inaccurate[3,4]. Intraoperative ultrasonography provides more precise information but could

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be performed only at laparotomy. The technique described allows accurate hepatic staging to be undertaken without the need for laparotomy. In six of seven patients unexpected intrahepatic disease was detected. In four patients laparoscopic ultrasonography provided diagnostic information which would previously have been gained only at laparotomy.

A large-bore cannula to allow the introduction of currently available tried and tested ultrasonographic probes has been developed. Future developments will include the use of smaller diameter side-viewing and flexible probes which may permit the staging of pancreatic tumours and the detection of choledocholithiasis[5].

Acknowledgements

The authors would like to thank Oxylitre for their development of the large cannula and Keymed for supplying the ultrasonography equipment.

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Bioelectrical impedance analysis in the measurement of the body composition of surgical patients

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The evaluation of nutritional status in surgical patients remains a difficult problem. Bioelectrical impedance analysis (BIA) is a new method of body composition analysis which is easily performed at the bedside. This study determined the accuracy of BIA in the measurement of total body water (TBW) and potassium (TBK) in a heterogeneous group of surgical patients. The resistance and reactance components of impedance were measured with a whole body impedance analyser. Tritiated water dilution and whole body monitoring were the reference methods for TBW and TBK analysis. With the BIA technique the coefficient of variation for the estimation of TBW was 8·1 per cent and for TBK was 6·4 per cent. Allowing for the errors of the reference methods these results show that BIA is of limited value in the estimation of TBW but may provide a useful index of TBK.

The nutritional assessment of hospital patients remains difficult[1,2]. This applies to the identification of patients at risk from protein or energy undernutrition and the assessment of the effects of nutritional intervention. A variety of nutrition-related variables (e.g. serum albumin, delayed cutaneous hypersensitivity) have been evaluated but their use has been limited because they are influenced by factors independent of the patient's nutritional status[3,4].

Various methods of body composition analysis have been tested[5] to provide direct estimates of patients' energy (fat) and somatic protein (skeletal muscle) reserves. Anthropometry (skinfold thickness or arm muscle circumference) may not be accurate in patients with subcutaneous oedema and may lack the precision to assess the effects of nutritional intervention[5]. It is not clear whether the body compartments identified by these methods are the most relevant markers of metabolic mass or nutritional status.

The body cell mass was defined by Moore *et al.*[6] as 'that component of body composition containing the oxygen exchanging, potassium rich, glucose oxidizing, work performing tissue'. As the compartment responsible for vital processes such as heat production and protein synthesis it is, perhaps, the primary purpose of nutritional support to maintain this compartment and its functions. Since 98 per cent of total body potassium (TBK) is contained within cells, the measurement of TBK by whole body monitoring is a standard method of measuring the body cell mass[6]. In hospital patients determining the body cell mass from ^{40}K analysis is often impracticable. Bioelectrical impedance analysis (BIA) is readily applicable to the clinical setting and in normal volunteers provides an estimate of the mass and distribution of total body water (TBW)[7,8]. Lean body-mass may be measured in normal individuals with BIA[9] and combined with body habitus measurements may provide an estimate of body cell mass[10].

This study examines the ability of BIA to determine the mass and distribution of body water and the size of the body cell mass in a heterogeneous group of surgical patients.

Patients and methods

Patients

The clinical details and body habitus parameters of the patients undergoing estimation of TBW (isotope dilution method, $n = 43$) or TBK (whole body monitor, $n = 31$) are shown in *Tables 1* and *2*. All patients had total body resistance and reactance measured on the same day as reference methods of body composition. A subset ($n = 18$) of those who had TBW estimated by isotope dilution underwent measurement of extracellular water space. The intracellular water space was obtained by subtracting extracellular water from TBW. The ratio of extracellular to intracellular water space obtained by isotope dilution was compared with that obtained by BIA.

Bioelectrical impedance analysis

Impedance was determined using a four-terminal impedance analyser (RJL Systems, Detroit, USA). This battery-operated system passes a 50-kHz sinusoidal signal at a root mean square current of 800 μA. It incorporates phase-sensitive electronics which provides resistance and reactive components of total impedance.

Patients rested in a supine position. Gelled electrodes were placed on the dorsal surfaces of the hands and feet proximal to the metacarpophalangeal and metatarsophalangeal joints, between the

Table 1 *Diagnosis of patients undergoing analysis of either total body water or total body potassium*

	Total body water ($n = 43$)	Total body potassium ($n = 31$)
Colonic cancer	7	4
Other gastrointestinal cancer	7	5
Inflammatory bowel disease	14	14
Pancreatitis	7	2
Other benign gastrointestinal conditions	8	6

Table 2 *Body habitus parameters of patients undergoing analysis of either total body water or total body potassium*

	Total body water		Total body potassium	
	Men ($n = 24$)	Women ($n = 19$)	Men ($n = 16$)	Women ($n = 15$)
Age (years)	49(4)	45(4)	47(5)	44(6)
Height (cm)	173(1)	159(2)	172(2)	160(2)
Weight (kg)	62·6(2·6)	53·4(3·1)	65·3(2·6)	44·9(2·0)
Percentage of ideal body-weight	92(4)	91(5)	94(4)	79(3)
Percentage weight loss	10(2)	11(2)	10(2)	13(2)

Values are mean(s.e.m.)

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distal prominences of the radius and ulna at the wrist, and between the medial and lateral malleoli at the ankle. Calibration of the analyser was checked using a standard resistor.

Total body water volume

An intravenous injection of 2 MBq tritium-labelled water was allowed to equilibrate for 4 h before blood samples were obtained. Corrections were made for the fraction of dose excreted in urine. This technique has a precision of 1·5 per cent.

Extracellular water volume

[^{77}Br]sodium bromide (0·7 MBq) was administered intravenously and allowed to equilibrate for 24 h before blood samples were obtained. Corrections were made for urinary excretion of tracer, plasma protein levels and Gibbs–Donnan equilibrium.

Intracellular water volume

Intracellular water volume was obtained by subtracting extracellular water from TBW.

Total body potassium

This was measured externally by detection of 1·46-MeV γ-rays emitted from the naturally occurring radioactive isotope of ^{40}K which is a constant fraction (0·012 per cent) of body potassium. The shielded-room, scanning whole body monitor used a ring of six 15 × 75 cm sodium iodide crystal scintillation detectors. The counter was calibrated using phantoms ranging in weight from 30 to 90 kg and containing known activities of ^{40}K. Each subject was scanned for 2000 s.

Anthropometry

Height and weight were measured on beam balance scales.

Plasma potassium concentration

Plasma potassium concentration was measured on a multichannel analyser (SMC II; Technicon, Tarrytown, New York, USA).

Statistical analysis

A multiple correlation matrix was applied to the TBW, TBK, resistance, reactance, age, height, height^2, weight and plasma potassium concentration. A 5 per cent level of significance was used for all data analyses. A multiple stepwise regression was performed using TBW or TBK as the independent variables. For each regression the correlation coefficient and standard error of the estimate (s.e.e.) were obtained. The combination of impedance and body habitus factors which gave the smallest s.e.e. was established.

Results

The result of a stepwise regression analysis relating TBW (in litres) to body-weight (W in kilograms), height (H in centimetres) and resistance (R in ohms) is shown in *Table 3*. The prediction equation with the lowest s.e.e. and highest correlation coefficient (r) was:

$$\text{TBW (BIA)} = 0{\cdot}208\text{W} + 0{\cdot}275\text{H} - 0{\cdot}0299\text{R} - 10{\cdot}81$$

Reactance and plasma potassium concentration did not contribute to the predictive value of the equation. The relationship between TBW derived from body habitus measurements/BIA and that measured by isotope dilution is shown in *Figure 1*. The mean(s.d.) value for the ratio of extracellular to intracellular water space measured by isotope dilution was 0·9(0·3) (range 0·5–1·6; $n = 18$). Resistance, reactance and body habitus measurements could not predict

Table 3 *Results of stepwise regression analysis relating total body water as measured by isotope dilution methods to body-weight, height and resistance*

	Standard error of the estimate (litres)	Coefficient of variation (%)	r
W	3·8	11·3	0·841
W + H	3·3	9·8	0·886
W + H + R	2·7	8·1	0·926

W, body-weight (kg); H, height (cm); R, resistance (ohms)

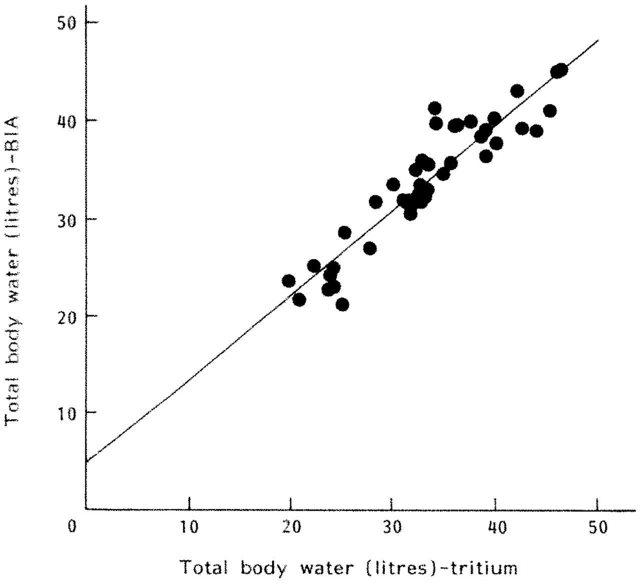

Figure 1 *Relationship between total body water derived from bioelectrical impedance analysis (BIA)/body habitus measurements and that measured by isotope dilution methodology (see* Patients and methods) *in a heterogeneous group of surgical patients* (n = *43*). $r^2 = 0{\cdot}862$, $y = 6{\cdot}604 + 0{\cdot}940x$

Table 4 *Results of stepwise regression relating total body potassium as measured by whole body monitoring to height^2, weight, resistance, reactance, plasma potassium and age*

	Standard error of the estimate (g)	Coefficient of variation (%)	r
H^2	14·9	15·2	0·856
$H^2 + W$	11·2	11·4	0·925
$H^2 + W + R$	10·3	10·5	0·939
$H^2 + W + R + X_c$	7·3	7·4	0·971
$H^2 + W + R + X_c + K$	6·7	6·8	0·976
$H^2 + W + R + X_c + K + A$	6·3	6·4	0·980

H^2, height^2 (cm^2); W, weight (kg); R, resistance (ohms); X_c, reactance (ohms); K, potassium (mmol/l); A, age (years)

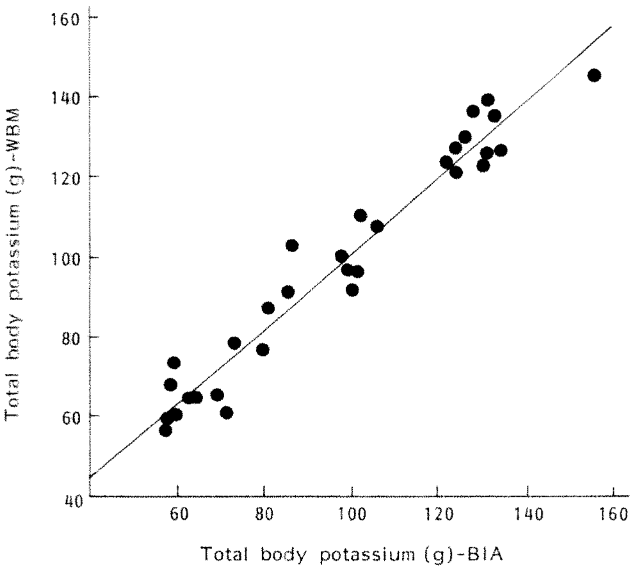

Figure 2 *Relationship between total body potassium (an index of body cell mass) derived from bioelectrical impedance analysis (BIA)/body habitus measurements and that measured by whole body monitoring (WBM) (see* Patients and methods) *in a heterogeneous group of surgical patients* (n = *31*). $r^2 = 0{\cdot}948$, $y = 4{\cdot}431 + 0{\cdot}868x$

the distribution of water between extracellular and intracellular compartments (coefficient of variation >25 per cent).

The result of a stepwise regression relating TBK to height^2 (H^2 in square centimetres), weight (W in kilograms), resistance (R in ohms), reactance (X_c in ohms), plasma potassium concentration (K in millimoles per litre) and age (A in years) is shown in *Table 4*. The prediction equation with the lowest s.e.e. and highest *r* value was:

$$\text{TBK (BIA)} = 0{\cdot}0055\text{H}^2 - 0{\cdot}0597\text{W} - 0{\cdot}1783\text{R} + 1{\cdot}22X_c - 11{\cdot}475\text{K} + 0{\cdot}2203\text{A} + 29{\cdot}184$$

The relationship between TBK derived from body habitus measurements/BIA and that measured by whole body monitoring is shown in *Figure 2*.

Discussion

These results suggest that in a heterogeneous group of surgical patients TBW can be estimated from body habitus parameters/BIA with a coefficient of variation of 8·1 per cent (*Table 3*). This is comparable to the results (5–6 per cent) of Schroeder *et al.* who measured TBW in a similar group of patients[11]. The error is, however, much greater than that described for healthy individuals (3–4 per cent)[10]. The greater error in this study probably relates to changes in fluid and electrolyte composition in surgical patients which may alter the conductivity of body compartments.

If the hydration of lean tissue is constant, the proportion of fat and lean tissue in the body can be derived from measurements of TBW. If BIA accurately predicts TBW, this technique might allow assessment of fat mass and lean body-mass in health and disease[8,11]. This study shows that BIA does not accurately measure TBW in sick surgical patients and it is impossible to assume that the lean tissue of such patients contains a fixed proportion of water. BIA cannot measure accurately the fat mass and lean body-mass of such patients.

Previous studies[10] have shown that the body cell mass of healthy individuals can be predicted from height and resistance alone (coefficient of variation 6 per cent). In the present study a similar coefficient of variation (6·4 per cent, *Table 4*) was achieved in surgical patients using a predictive equation to which reactance, plasma potassium concentration and the patient's age had been added. It has been suggested that of the two components that make up impedance, resistance relates closely to body water and reactance to the membrane mass[8]. Patients with malnutrition may become relatively potassium depleted[12] and the need to include additional factors such as reactance and plasma potassium concentration may reflect alterations of electrolyte and membrane status which can occur in ill or malnourished patients.

The reference methods of body composition analysis used in this study carry errors of their own. Tritium dilution for TBW has a precision of 1–2 per cent and, as a result of hydrogen exchange, may systematically overestimate TBW by up to 2 per cent[5]. These errors were small in relation to that which was observed when BIA/body habitus parameters were used to predict TBW (8·1 per cent). In contrast, whole body montoring is less precise (2–4 per cent) in the estimation of TBK[13]. This error is not insubstantial compared with the coefficient of variation noted in the present study using BIA/body habitus parameters to predict TBK (6·4 per cent). The error attributable solely to BIA in predicting TBK may be substantially less than the coefficient of variation would suggest (*Table 4*). From the known reproducibility of the individual parameters in the predictive equation, the reproducibility of estimating TBK from this equation is less than 3 per cent. BIA cannot, therefore, detect the small changes in body composition that might be observed with a short period of nutritional support. BIA may be useful as a 'field' method for defining the characteristics of a group of patients under study or as a method to follow large changes in body composition in patients undergoing prolonged nutritional support.

Shizgal[8] proposed that the ratio of total body exchangeable sodium to exchangeable potassium (Na_e:K_e) might be a suitable method of assessing nutritional status. This ratio is effectively the extracellular mass expressed as a function of the metabolically active body cell mass. In malnutrition this ratio will increase as there is a reduction in the body cell mass accompanied by a relative and actual increase in the extracellular space. Tellado *et al.*[14] have shown that Na_e:K_e identifies malnourished patients at risk of dying with an accuracy of >85 per cent. In the present study, isotope dilution methods were used to estimate the ratio of extracellular to intracellular water in a small group of patients. A wide range of values was obtained, consistent with the varied clinical condition of the patients. It has been suggested that BIA performed at a fixed frequency can resolve the body fat-free mass into extracellular and intracellular compartments[8]. In the current analysis, however, based on fixed-frequency impedance/body habitus parameters it was not possible to predict the ratio of extracellular to intracellular water. It has, however, been reported that low frequency current (<10 kHz) conducts mainly through extracellular fluid, while high frequency current (>1 MHz) conducts through the intracellular and extracellular fluid space[15]. It may be possible to use multifrequency BIA techniques to resolve extracellular from intracellular body compartments.

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Persistence of allogeneic cells in graft and host tissues after small bowel transplantation

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Small bowel transplantation is associated with a significant risk of graft versus *host disease owing to the large amount of organized lymphoid tissue within the graft. This study assessed whether graft lymphoid cells could persist in the long term following fully allogeneic small bowel transplantation when graft rejection was prevented by cyclosporin immunosuppression. Transplantation was carried out between PVG and DA strains of rat. Cyclosporin (15 mg/kg) was given daily from transplantation, and groups of animals were studied at 28 and 56 days after grafting. The proportions of donor- and recipient-derived cells in the graft and in the host gut and lymphoid tissues were assessed using immunohistochemical tissue staining and monoclonal antibodies specific for cells expressing class I antigens from the two strains of rat. Results demonstrated a persisting population of graft-derived T cells which were capable of migration to the host. Therefore, there may be a long-term risk of graft* versus *host disease after small bowel transplantation under cyclosporin immunosuppression.*

Unlike other vascularized organ grafts, small bowel transplants inevitably include large amounts of organized lymphoid tissue, both within the gut wall (mucosa and Peyer's patches) and in the mesenteric lymph nodes. After small bowel transplantation, host lymphocytes migrate to graft mucosa, Peyer's patches and mesenteric nodes[1]. Similarly graft lymphocytes, if not destroyed by host cells, can migrate into host lymphoid tissues. Extensive bidirectional cell migration between graft and host tissues for up to 1 week after intestinal transplantation has previously been shown[2]. The migration of graft cells to host tissues was enhanced when cyclosporin inmunosuppression was used to prevent graft rejection.

The aim of this study was to determine whether a population of graft-derived leucocytes persists after small bowel transplantation, or whether these cells become completely replaced by those of host origin. If graft-derived cells persist there may be a continuing risk of graft *versus* host disease (GVHD) in immunosuppressed recipients.

Materials and methods

Transplant model

Fully allogeneic heterotopic vascularized small bowel transplantation was carried out between two genetically dissimilar inbred strains of rat (PVG donors and DA recipients)[3]. The native intestine of the recipient was not disturbed and the two ends of each graft were exteriorized as stomas. This model allows assessment of the immunological consequences of transplantation without compromising the nutritional status of the recipient, which might itself have an effect on the immunological response. All recipients were given cyclosporin, 15 mg/kg daily by gavage, from the day of operation to prevent graft rejection. Clinical evidence of rejection[4] or GVHD[5,6] was sought daily. Groups were studied at 28 and 56 days after transplantation. At these times host and graft lymphoid tissues were harvested, snap-frozen and stored at −70°C.

Immunohistochemistry

Tissues were subjected to immunohistochemical staining using an indirect immunoperoxidase technique[7]. Monoclonal antibodies MN4 and OX27, which are specific for the major histocompatibility class I antigens expressed by cells of DA and PVG rats respectively, were used to identify cells of donor origin within host tissues and host cells within the graft[7,8]. There is no cross-reactivity between these two antibodies. Tissues studied included graft and host intestinal mucosa, Peyer's patches and mesenteric nodes, and host spleen, peripheral lymph nodes, liver and thymus. Comparison of the results obtained with each of the two antibodies enabled accurate determination of the proportions of graft and host cells in each tissue.

Assessment of cell numbers

Representative sections of each host and graft tissue were studied. The number of allogeneic cells present (graft cells in host tissues, host cells in graft tissues) was counted using a Whipple grid and expressed as a percentage of the total number of cells present. Three high power fields were counted for each section. Six animals were included in each group. Unless otherwise stated values are expressed as median (range).

Results

Under cyclosporin immunosuppression all animals thrived with no clinical or histological evidence of rejection or GVHD.

Host cells within the graft

Immunohistochemical staining demonstrated extensive replacement of graft tissues by cells of host origin. The cellular component of the mesenteric nodes was completely replaced by host cells, with only the stroma remaining of graft origin. The T cell areas (dome) of the graft Peyer's patches were extensively replaced by host cells such that more than half of the cells in these tissues were of host origin. In contrast the B cell areas (follicles) contained fewer than 5 per cent of host-derived cells (*Figure 1*). In the small bowel mucosa about 50 per cent of the cells in the lamina propria were of host origin whereas all of the enterocytes remained of graft origin (*Figure 2*). There was no significant difference between the degree of host cell infiltration of the graft when assessed at days 28 or 56.

Graft cells within the host

Graft cells were identified in the host lamina propria, Peyer's patches, mesenteric nodes, spleen and peripheral lymph nodes at days 28 and 56 after small bowel transplantation. The proportion of graft cells in these tissues was much smaller (5–20 per cent) than that of host cells within the graft (*Figure 3*). In the periarteriolar lymphatic sheaths in the spleen the proportion of graft cells was 3 (1–7) per cent at 28 days and 8 (5–13) per cent at 56 days. In the peripheral lymph node the corresponding figures were 9 (8–12) per cent at 28 days

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and 14 (8–19) per cent at 56 days after transplantation. No graft-derived cells could be detected in the host liver or thymus at either time.

Where graft cells were found, consecutive 8-μm tissue sections were stained with the monoclonal antibody which identifies graft cells and the monoclonal antibody OX19 which recognizes the CD5 receptor present on virtually all mature T lymphocytes. The positive graft cell staining corresponded with that for T lymphocytes, implying that the graft cells in the host tissues were T cells.

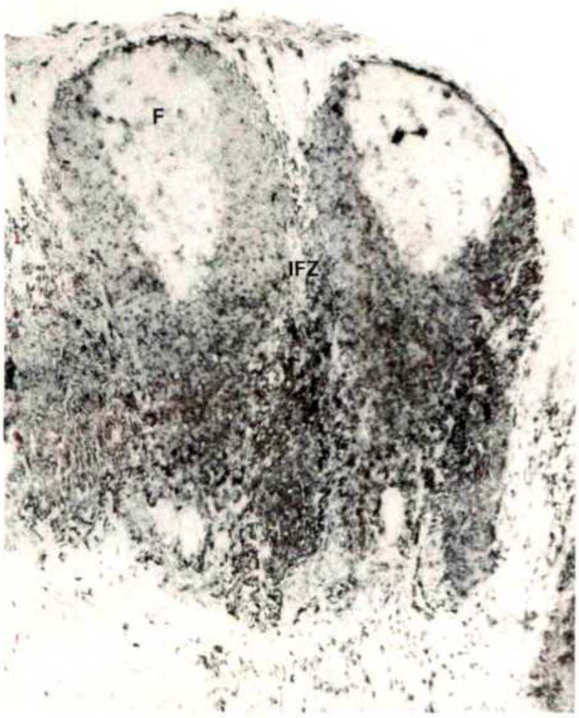

Figure 1 *Photomicrograph showing the distribution of host cells within graft Peyer's patch to demonstrate preferential localization to the interfollicular zone. F, follicle; IFZ, interfollicular zone. (Indirect immunoperoxidase and haematoxylin stain, original magnification × 80)*

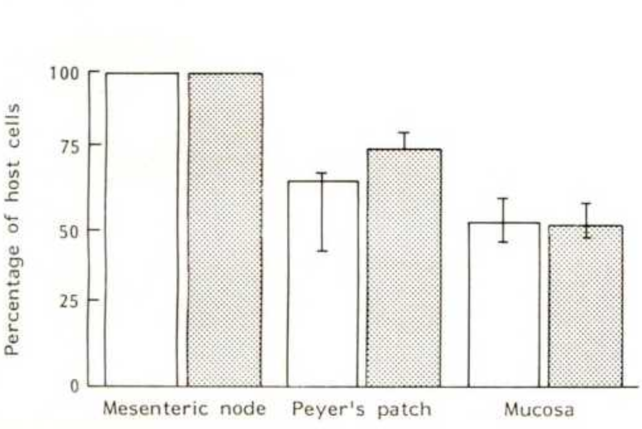

Figure 2 *Infiltration of the small bowel graft by host cells after 28 (□) and 56 (▨) days. Values are median (range); n = 6 for each group. Mucosal infiltration was significantly less than Peyer's patch infiltration, which was significantly less than mesenteric node infiltration ($P < 0.05$ for each, Wilcoxon rank sum test)*

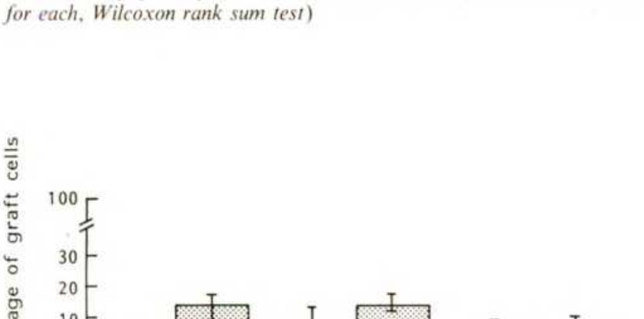

Figure 3 *Infiltration of recipients' intestinal tissues by graft cells after 28 (□) and 56 (▨) days. Values are median (range); n = 6 for each group. There were no significant differences between the groups (Wilcoxon rank sum test)*

Discussion

Previous studies using this model have shown that graft cells migrate to host tissues within 24 h of transplantation. However, in the absence of immunosuppression the infiltrating graft cells disappear by day 5, as acute rejection destroys graft lymphocytes and the graft mucosa[2]. If acute rejection is prevented by cyclosporin treatment, then large numbers of graft cells are found in host tissues 7 days after transplantation[2].

In the present study cyclosporin was administered to two groups of animals for either 28 or 56 days after transplantation, at which time the tissues were harvested. By 56 days the tolerizing process should be well established[9]. It was not known whether host cells would completely repopulate the graft or whether a steady state would be achieved with a population of graft leucocytes surviving indefinitely. The results demonstrate that cells of donor origin, which are probably T lymphocytes, persist for at least 56 days after transplantation.

The distribution of graft cells within host tissues may reflect the lymphatic and venous drainage of the graft. This study was unable to identify graft cells in the liver or thymus, but did detect them in the spleen, peripheral lymph nodes and parathymic nodes. The transplant model used in this study involves anastomosis of the graft portal vein to the host inferior vena cava, which results in the venous drainage bypassing the liver[3]. Lymphatic drainage of the graft is re-established by 14 days after transplantation[10] and cells re-enter the circulation via the thoracic duct[11].

Immunocompetent T lymphocytes of donor origin are necessary for the development of GVHD[11,12]. It has previously been shown in short-term studies that allogeneic cells could be detected in the T cell areas of graft and host lymphoid tissues[13]. The current work shows that T lymphocytes of donor origin persist in host tissues in the long term after small bowel transplantation under cyclosporin immunosuppression.

In this model, during continuous cyclosporin immunosuppression there was no clinical or histological evidence of GVHD. However, previous work has demonstrated a potential for graft *versus* host reactivity by cells originating in PVG tissues towards DA strain recipients. When transplantation is carried out from PVG donors to (PVG × DA) F_1 hybrid recipients, no rejection occurs because the F_1 hybrid shares all potential histocompatibility antigens with the parental strain[3,5]. In this model, GVHD proceeds unchecked and leads to recipient death approximately 21 days after transplantation[14]. In other rat strain combinations fully allogeneic small bowel transplantation can result in the development of overt GVHD[15].

The prolonged survival of graft cells in host tissues may be due to an inability of host lymphocytes to destroy the allogeneic cells in the presence of immunosuppression. Recently cases of human transplantation have been carried out using FK506 (Fujisawa, Japan) as immunosuppressant. In these patients graft-derived cells could be detected in the recipient lamina propria in the early period after transplantation but gradually declined to zero (around 50 per cent of all cells in the lamina propria at day 28, 10 per cent at day 60, zero by day 70)[16]. Overt GVHD has been described after human small bowel transplantation using conventional immunosuppressive regimens such as combined cyclosporin, azathioprine and prednisolone[17,18]. In addition, donor lymphocytes have been detected in the recipient's peripheral blood[16,19].

In conclusion, in a rat model of fully allogeneic small bowel transplantation, using cyclosporin to prevent graft rejection, a population of graft-derived T lymphocytes persists for at least 56 days in certain host tissues. Therefore, in addition to the known risk of rejection, there may also be a continuing potential for GVHD after small bowel transplantation.

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Effect of phosphatidylcholine on postoperative adhesions after small bowel anastomosis in the rat

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The possibility of preventing postoperative adhesions using phosphatidylcholine (PC) was studied in rats. A small bowel anastomosis was created using continuous or interrupted 5/0 silk sutures. Adhesions were measured by recording the maximal length of adhesions around the anastomosis and the number of organs involved in the adhesions. PC was administered intraperitoneally either as a single dose or as three separate doses. Postoperative adhesions developed in all animals; the degree of adhesion was independent of the suture technique used. PC given once at a dose of 20 mg significantly decreased adhesion formation ($P < 0.01$)*. The mechanism underlying this effect may be that the exogenous PC provides a lubricant layer replacing endogenous hydrolysed phospholipid. The result with repeated PC administration was not different from that after a single dose. Increasing the single dose of PC to 40 or 60 mg resulted in anastomotic dehiscence and subsequent peritonitis. It is concluded that PC in a single dose of 20 mg reduces adhesion formation after small bowel anastomosis in the rat.*

Intra-abdominal adhesions are the major cause of small bowel obstruction[1]. The most common cause of adhesion formation is surgery[2]. Previous attempts at reducing the incidence of adhesions after operation have been based on improving the physical mobility of the viscera[3-8], prokinetic agents such as cisapride[9], or various enzymes or anti-inflammatory drugs[10-12]. All these attempts have failed despite extensive trials. Phosphatidylcholine (PC) was recently shown to reduce the formation of adhesions after operation in four different models in the rat[13]. This encouraging result warrants further investigation and the present study examines the possible protective effect of PC on adhesion formation after small bowel anastomosis in this animal. The model employed is of special interest because anastomotic surgery is common in clinical practice.

Materials and methods

Animals

Sprague-Dawley rats of mean(s.d.) weight 250(20) g were purchased from Møllegard, Skensved, Denmark and fed a standard pellet diet and tap water *ad libitum* before and after surgery.

Surgical technique

Animals were anaesthetized with ether and shaved before the operation which was performed with clean but not sterile instruments. Skin was cleaned using 0·5 per cent chlorhexidine in 70 per cent ethanol. The abdomen was opened through a midline incision and the terminal ileum and caecum with ascending colon were exposed. Tissues were handled gently and microsurgical instruments were used. The anastomosis was created in the ileum 2 cm proximal to the ileocaecal junction using 5/0 silk sutures. Two kinds of suture technique were used, either continuous or eight interrupted sutures. After this procedure, PC (Lipostabil; A. Natterman, Cologne, Germany) was instilled into the abdominal cavity, which was then closed in two layers using 3/0 silk sutures.

Experiments

The animals were distributed in nine groups as shown in *Table 1*. When the single dose of PC was used, it was instilled at the time of closure of the abdomen. In groups given three doses of PC two additional doses were given intraperitoneally on the first and second days after operation. The volume load per dose was 2 ml. Control animals received 2 ml saline intraperitoneally at closure of the abdomen and on the first and second days after operation.

Adhesions were evaluated blindly at 7 days after operation using a wide U shaped subcostal incision after the animals had been killed by an overdose of ether. The number of organs involved in adhesions was recorded and the maximal length of ileum entrapped in adhesions around the anastomosis was measured.

Statistics

Values are given as mean(s.e.m.). Student's t test was used for statistical analysis of maximal adhesion length. The χ^2 test was used for evaluation of organ involvement in adhesions.

Results

Effect of surgical technique on adhesion formation

No difference was seen in adhesion formation related to the continuous *versus* the interrupted suture technique (*Table 1*). The mean(s.e.m.) maximal length of ileum entrapped in adhesions was 22·3(4·0) mm when the anastomosis was closed with continuous sutures and 22·1(6·1) mm when it was closed with eight interrupted sutures.

Effect of single-dose phosphatidylcholine on adhesion formation

Adhesion formation was significantly decreased by 20 mg PC given intraperitoneally once at the end of the operation. The maximal length of ileum entrapped in adhesions decreased from 22·3(4·0) mm in control rats to 12·0(2·4) mm in animals with continuous suture bowel anastomosis ($P < 0.01$). Similarly, the length decreased from 22·1(6·1) mm in controls to 12·3(1·9) mm in rats with interrupted suture anastomoses ($P < 0.001$). Furthermore, the degree of involvement of small intestine in the adhesions decreased significantly ($P < 0.001$) in PC-treated rats, irrespective of the suture technique.

Increasing the dose of PC to 40 or 60 mg did not further improve adhesion prevention, but instead resulted in complications. After 40 mg PC given once at the end of the operation there was a 10 per cent mortality rate, and in three of 20 animals anastomotic dehiscence resulting in peritonitis was seen. After increasing the single dose of PC to 60 mg at the end of laparotomy, four of ten rats died from peritonitis caused by anastomotic dehiscence and one animal had florid peritonitis when killed on the seventh day after operation. The maximal length of ileum entrapped in adhesions in surviving animals in this group was 13·3(3·0) mm.

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Table 1 *Effect of phosphatidylcholine on adhesion formation*

Dose of PC	No. of animals	Suture technique	Mean(s.e.m.) maximal length of adhesions (mm)	Organ involvement in adhesion						Comments
				Small intestine	Omentum	Caecum	Fat pad	Ascending colon	Anterior wall	
Control	20	Continuous	22·3(4·0)	13	6	13	5	0	0	
20 mg × 1	10	Continuous	12·0(2·4)*	4†	8	6	5	1	0	
40 mg × 1	10	Continuous	18·1(4·9)	9	6	9	1	2	2	2 dehiscences of anastomosis and peritonitis
60 mg × 1	10	Continuous	13·3(3·0)*	6	3	4	2	3	2	5 dehiscences of anastomosis
20 mg × 3	15	Continuous	11·2(2·2)†	3†	9	7	5	1	0	
Control	20	Interrupted	22·1(6·1)	14	5	14	6	0	0	
20 mg × 1	10	Interrupted	12·3(1·9)†	4†	6	6	2	1	0	
40 mg × 1	10	Interrupted	18·7(3·9)	6	6	8	4	4	0	1 dehiscence of anastomosis and peritonitis
20 mg × 3	15	Interrupted	10·7(3·5)†	3†	9	7	7	0	0	

Values for organ involvement are numbers of animals with adhesions involving the respective organs. PC, phosphatidylcholine; $*P < 0{\cdot}01$; $\dagger P < 0{\cdot}001$ (*versus* appropriate control, Student's *t* test for maximal adhesion length and χ^2 test for organ involvement)

Effect of three doses of phosphatidylcholine on adhesion formation

Administration of 20 mg PC at the end of the operation and on the first and second days after operation did not improve the maximal length of ileum entrapped in adhesions and did not decrease the involvement of the small intestine in adhesions, compared with a single dose (*Table 1*).

Discussion

Intra-abdominal adhesions are due mainly to previous surgery and they are the major cause of small bowel obstruction[1,2]. Although anastomotic surgery is common in clinical practice, the contribution of an anastomosis to the production of adhesions has not yet been elucidated[9,14]. It is well known that healing of an anastomosis involves several steps. First, an acute inflammation occurs, followed by proliferation of fibroblasts. These produce collagen which is later remodelled[15]. It has been suggested that ischaemic tissue is the main cause of adhesions[16], and it has been shown that the perianastomotic oxygen tension is lower with the continuous suture technique than with interrupted sutures[17]. It would seem, therefore, that an anastomosis created using continuous sutures should cause more adhesions than one created using interrupted sutures. However, in the present study no difference was found in the degree of adhesions between the two suture techniques. This suggests that oxygen tension is not the only factor in adhesion formation after surgery. The use of silk as suture material and clean but not sterile instruments in this study may be the reason for the large number of adhesions that formed around the small bowel anastomosis.

In a previous report it was shown that PC decreased intra-abdominal adhesion formation in four different adhesion models in the rat[13]. However, in that report the clinically important perianastomotic adhesions were not studied. In the present investigation it has been shown that a single dose of PC decreased adhesion formation after small bowel anastomosis; a dose of 20 mg was used because this has previously been shown to be effective in preventing adhesion formation in the rat[13].

The mechanism underlying this effect of PC is unknown. The critical event in adhesion formation is the failure of the peritoneum to remove deposited fibrin. The peritoneum normally possesses fibrinolytic properties through plasminogen activators[18,19]. Adhesions seen after peritoneal injury are associated with depression of plasminogen activator activity[18,19]. Furthermore, topical application of tissue plasminogen activator has been shown to prevent adhesion formation[20]. Therefore, one might speculate that the beneficial effect of exogenous phospholipid on adhesion formation is through activating plasminogen. It is, however, more likely that PC reduces adhesion formation by providing a lubricant layer. PC is the main constituent of the surface-active material which coats the peritoneal membrane[21], and it adheres to peritoneum and is held in place by binding of its positively charged choline residue to the negatively charged peritoneum[21]. It is likely that the endogenous PC is hydrolysed by activated phospholipases during anastomotic healing, since phospholipase A_2 activity has been demonstrated in leucocytes and in inflammatory ascitic fluid in rabbits[22], as well as in ischaemic tissue[23,24]. The exogenously administered PC might then replace the hydrolysed endogenous PC.

A single dose of 20 mg PC reduced the maximal length of adhesions and the involvement of the small intestine in them, but repeating PC at this dose daily for 2 subsequent days did not further improve the effect. This suggests that it is sufficient to give PC only once at the time of surgery for an optimal effect, provided that the correct dose is used. Increasing the dose of PC to 40 or 60 mg resulted in deaths and complications caused by anastomotic dehiscence and peritonitis. It could be speculated that these high doses of PC reduced the normal adhesion formation that is desirable and necessary for normal anastomotic healing. This would be consistent with the demonstration that when omentum is prevented from coming into contact with an anastomosis there is a 100 per cent leakage rate[25]. Furthermore, wrapping an anastomosis in viable omentum significantly decreases the leakage rate[26]. Since the real problem presented by adhesions is small bowel obstruction[1,2], and since a single dose of 20 mg PC reduced the involvement of the small bowel in adhesions, PC might offer a useful means of adhesion prevention.

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Audit of general practitioner referrals to an acute surgical unit

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One hundred and ninety referrals from general practitioners (GPs) to an acute surgical unit were audited prospectively over a 6-month period. A total of 78 admissions were considered inappropriate of whom 23 patients were thought to have needed neither surgical admission nor opinion. The estimated expenditure resulting from admissions deemed inappropriate was £25 000. The daytime commitments of more senior staff on routine emergency duty days meant they were not easily available to deal with calls concerning acute GP referrals. These admissions reduce the efficiency of the service; this may be improved by a senior member of the team accepting and screening GP calls.

The current practice at this hospital is for the duty preregistration house officer to accept telephone referrals and arrange admission for acute surgical patients referred by general practitioners (GPs). More senior members of the duty surgical team are not involved in accepting referrals unless specifically requested by the house officer or GP. This arrangement prompted a prospective audit of the mechanism of referral, and the cost-effectiveness and utilization of acute surgical facilities.

The value of surgical audit in quality assurance[1,2] and allocation of surgical resources has been notable[3,4]. Emergency admissions may reduce the efficiency of the service by impeding the treatment of elective cases[5]. Significant financial consequences may arise from inappropriate acute admissions.

Problems may be envisaged when patients lie beween the extremes of those requiring acute surgical intervention and those needing only elective outpatient opinion. At this hospital there is no current policy for the ready provision of a senior surgical opinion in determining the need for admission.

Unnecessary admissions not only result in a waste of resources, but may also lead to cancellation of elective cases if beds are unavailable. This could cause loss of revenue if contracts to provide service are not fulfilled.

Patients and methods

From 1 August 1990 to 31 January 1991 all urgent GP referrals to an acute general surgical unit at this hospital were audited prospectively. The unit comprised two consultant surgeons, one senior registrar, one registrar, two senior house officers and two preregistration house officers and was based on a 30-bed adult ward. Paediatric cases were admitted to a separate paediatric surgical ward.

The following groups of patients referred by GPs were excluded: patients referred to the accident and emergency department who required surgical admission; patients admitted from the outpatient clinic; and non-acute cases who were admitted after arrangement with the unit. All urgent GP referrals included were accepted on the unit's emergency duty days.

Referral calls were taken by the preregistration house officer and all patients were admitted directly to the surgical ward. An audit form was completed for each patient and included demographic details, time of referral, name of GP referring, and the reason for referral.

Each patient was reviewed by the senior registrar who made and recorded a provisional diagnosis. After this initial assessment, the admission was determined as either appropriate to an acute surgical unit or inappropriate, and this categorization was reviewed by the senior registrar before discharge from hospital. The appropriateness of the referral was not confirmed by the consultants on the firm. An admission was deemed inappropriate if it was considered that the patient did not require acute general surgical care, although it was recognized that in most cases a general surgical opinion was necessary. Inappropriate admissions were grouped into what was considered the most appropriate referral category (*Table 1*).

The audit process did not influence the routine admission procedure, subsequent management or treatment. Investigations were requested by the preregistration house staff according to unit policy. All adult admissions with acute abdominal pain underwent investigations which included full blood count, serum urea, electrolytes and amylase, chest and abdominal radiography, and urine microscopy and culture.

Table 1 *Categories of admissions considered inappropriate*

1. Admission necessary but to a different speciality
2. Surgical opinion necessary but admission not (i.e. opinion in accident and emergency/admission ward)
3. Outpatient appointment required
    Urgent (less than 1 week)
    Routine
4. Surgical advice via telephone required
5. No opinion or advice necessary

Table 2 *Estimated costs used to calculate expenditure*

Item	Cost (£)
Urgent investigations	
Full blood count	17·00
Urea and electrolyte tests	12·00
Urine microscopy	10·00
Chest and abdominal radiography	40·00 (each)
Bed stay per day	150·00

The estimated costs of all admissions were calculated by adding costs of investigations and hospital stay (*Table 2*). These figures represent minimum expenditure and are not an accurate determination of total cost.

In cases where discharge was delayed, the reasons and length of stay were noted in order to distinguish costs incurred from this cause.

Results

One hundred and ninety patients were admitted to this surgical unit as urgent referrals from local GPs during the 6-month study. Of these 152 (80 per cent) were adults and 38 (20 per cent) were children. There were 142 males (75 per cent, age range 1–81 years) and 48 females (25 per cent, age range 2 months to 88 years).

A total of 78 admissions of 190 were deemed inappropriate. Of inappropriate admissions 79 per cent (62 of 78) were referred by their own GP, 18 per cent (14 of 78) were referred by a partner in the practice and only 3 per cent (two of 78) were referred by a deputizing service.

The majority of patients (111 of 190; 58 per cent) were admitted during working hours (8.00–18.00 hours); 38 per cent (72 of 190) were admitted between 18.00 and 24.00 hours, and only 4 per cent (seven of 190) were admitted after 24.00 hours.

Analysis of the 78 admissions deemed inappropriate reveals that: 26 per cent (20 of 78) were thought to need admission

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Table 3 *Diagnosis of inappropriate admissions*

General practitioner diagnoses			
Appendicitis	37	Pilonidal abscess	1
Abdominal pain (cause unknown)	27	Groin pain	1
		Breast abscess	1
Strangulated hernia	5	Femoral embolus	1
Urinary retention	2	Acute foot ischaemia	1
Irreducible rectal prolapse	2		
Senior registrar diagnoses			
Non-specific abdominal pain	26	No clinical problem	2
		Acute myocardial infarct	1
Constipation	13	Acute renal failure	1
Gynaecological*	6	Pilonidal sinus	1
Gastroenteritis	5	Renal colic	1
Urinary tract infection	4	Pneumonia	1
Non-strangulated hernia	4	Resolving mastitis	1
Biliary colic	2	Cerebrovascular accident	1
Balanitis	2	Malaria	1
Viral infection	2	Chronic foot ischaemia	1
Reducible rectal prolapse	2	Epididymo-orchiditis	1

*Including pelvic inflammatory disease, ectopic pregnancy, torted ovarian cyst

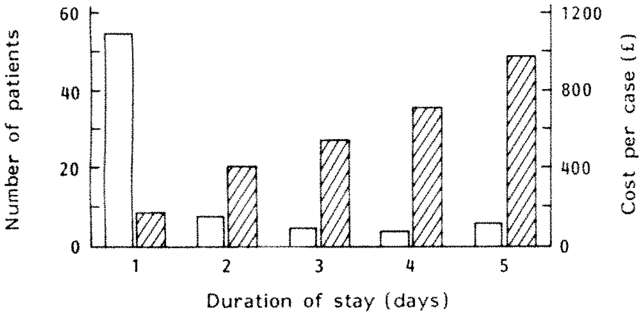

Figure 1 *Duration of stay and cost per patient for inappropriate admissions.* □, *Number of patients;* ▨, *cost per case*

but to a different speciality (eight paediatric, six medical and six gynaecological); 24 per cent (19 of 78) were thought to require surgical opinion in the accident and emergency department without admission; 10 per cent (eight of 78) required an urgent outpatient appointment and 8 per cent (six of 78) required a routine outpatient appointment; 3 per cent (two of 78) could have received advice over the telephone; and 29 per cent (23 of 78) were considered to need neither a surgical admission nor opinion. The diagnoses of the inappropriate admissions are listed in *Table 3*.

The mean cost per patient and duration of stay for admissions deemed inappropriate are shown in *Figure 1*. A total of 55 patients were admitted and stayed overnight, with a mean cost of £179 per patient; eight patients stayed 2 days and nights, the mean cost for these being £412 per patient. The cost of inpatient hospital care obviously increased with duration of stay, such that those patients admitted for 5 days and longer cost the unit approximately £1000 each. Ten patients who stayed 4 or more days did so for social reasons. The estimated total expenditure for those admissions considered inappropriate was approximately £25 000.

Discussion

Audit of surgical admissions has demonstrated that emergency cases can affect the rate of treatment of elective cases by reducing available beds, and therefore reduce the efficiency of the service[5]. Audit of the emergency surgical workload in Leicester has shown that improved casualty facilities have helped to reduce the number of surgical referrals for minor trauma[6]. This results in reduction of inappropriate referrals and therefore admissions and the efficiency of the surgical service is consequently improved.

No study has demonstrated whether any inefficiency exists in the system for admission of urgent GP referrals, what expenditure is incurred, and how the system could be improved.

Of the admissions in this study 78 were considered inappropriate but 41 of these patients needed some form of surgical opinion acutely but not after admission. This group of patients consists of 20 who required admission to another speciality, 19 who required an opinion in the accident and emergency department and the two patients who required surgical advice over the telephone. Outpatient appointments were required by 14 patients, and 23 needed no surgical opinion.

A total of 58 patients or 74 per cent of the inappropriate admissions and approximately 30 per cent of urgent referrals were thought not to need admission; this group consists of all inappropriate admissions except the 20 patients who required admission to a different speciality.

Analysis of theatre and outpatient commitments for the more senior surgical grades showed that an experienced member of the team was not easily available to deal with calls concerning emergency admissions for nine of 12 daytime sessions during the two routine emergency duty days. Senior members of the team were frequently involved with routine theatre lists and outpatient sessions during the emergency duty days and were not therefore providing an exclusively emergency service. All admissions subsequently considered inappropriate were accepted by the duty preregistration house officer, and commonly were not seen by a senior member of staff until after 17.00 hours, by which time investigations had already been performed.

Cost was seen to be directly proportional to the length of stay, and the majority of inappropriate admissions stayed overnight (55 of 78), with a mean cost of £179 each. Ten patients who stayed for 4 or more days did so because of social reasons, and the expenditure in these cases is not entirely due to inappropriate admission.

A senior member of the surgical team, such as a registrar or an experienced senior house officer, should be available to accept and screen GP calls. Where possible, this should involve shifting of routine commitments to days where the unit is not on emergency duty, such that a senior member of the team can be released without much disturbance to the routine service. This would provide GPs with experienced surgical advice, after which arrangements could be made to see patients in the accident and emergency department or admissions ward before admission. Alternatively, outpatient appointments could be made or patients could be redirected to the appropriate speciality. These measures would improve the efficiency of the service and reduce unnecessary admissions. Significant cost savings and improved patient care with more effective management could then be achieved.

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Management of colovesical fistulae associated with pelvic malignancy

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Thirteen patients with malignant colovesical fistulae are presented. The underlying pathology was cancer of the colon (seven cases), bladder (four cases) and cervix (two cases). The series demonstrates that wide surgical excision may be needed to achieve tumour clearance and that this may necessitate pelvic exenteration. Three patients who underwent inadequate tumour excision developed recurrence in the bladder, two with a fatal outcome. Wide excision of the bladder may be performed without urinary diversion by subtotal cystectomy and a reconstructive procedure. Substitution cystoplasty was performed on two patients at the time of tumour excision. Urinary tract involvement by such tumours is often extensive and optimal results may be achieved with a multidisciplinary approach.

In 1685 Wagner described the condition of excrementis alvi per penem ejectis[1] presumably due to the presence of a colovesical fistula. Today, objective evidence to confirm such a diagnosis remains difficult because the symptoms and investigations have a low sensitivity. Approximately 70 per cent of colovesical fistulae are due to diverticular disease and 15–20 per cent[2,3] are associated with a tumour of the colon or bladder.

Presenting symptoms most commonly arise from the urinary tract, although other complaints or findings may alert the clinician to the diagnosis. The classical findings of pneumaturia and mixed-growth urinary infection may be intermittent and one or both may be absent. Imaging techniques to confirm the diagnosis include plain radiography, cystography, intravenous urography, radionuclide monitoring of the urine following oral ingestion of ^{14}[C]polyethylene glycol[4] and a contrast enema study. The sensitivity of these tests is usually less than 50 per cent. Computed tomography may detect gas within the bladder in 87 per cent of cases[5] and has the advantage of providing information on the site and extent of bladder involvement. A colovesical fistula can be confirmed by the observation of pneumaturia following rigid sigmoidoscopy and air insufflation[6]. The fistula itself is rarely visualized. Combined cystoscopy and bimanual examination may reveal the site of the vesical opening of the fistula, the extent of a pelvic mass[7], and may provide histological confirmation of malignancy.

The operative management of malignant colovesical fistulae has varied over the years with discussion of the merits of single or multistaged resection[8]. McConnell *et al.*[9] reported ten malignant fistulae, of which only one was resectable and that patient died from pelvic sepsis after operation. More recently Krco *et al.*[10] reported only three long-term survivors of 14 patients with malignant fistulae, with seven receiving palliative diversion only, although Pollard *et al.*[2] reported that five of eight patients undergoing tumour resection survived for 5 years.

The choice of surgical procedure may be influenced by the presence of an abscess or intestinal obstruction, although in their absence a single-stage procedure is currently the favoured approach. There are a number of principles that should be considered in these patients, and these are illustrated by this study. Thirteen patients with colovesical fistulae secondary to malignant disease are reviewed with emphasis on the surgical management of the urinary tract and the potential for primary reconstruction of the intestinal and urinary tracts.

Patients and methods

Patients were referred for treatment between September 1988 and March 1991. There were eight men and five women with a mean age of 69 (range 46–84) years. The underlying causes of the fistulae are shown in *Table 1*. Eight of the patients were tertiary referrals, either because they had developed complications from initial surgical management such as recurrent fistula formation or local tumour recurrence, or because of extensive involvement of the urinary tract (*Table 2*). Seven of the group had previously undergone a course of external beam radiotherapy (EBRT), four for bladder cancer, two for cervical and one for colonic carcinoma.

Table 1 *Distribution of tumours in 13 patients with colovesical fistulae*

	Carcinoma		
	Colonic	Bladder	Cervical
Men	5	3	—
Women	2	1	2
Total	7	4	2

Table 2 *Pattern of referral*

Reason for referral	Site of primary
Complications of initial surgery (5)	
Recurrent fistula (2)	Bladder (1) Colon (1)
Recurrent tumour (in bladder) (3)	Colon (3)
Extensive involvement of the urinary tract (3)	Colon (1) Cervix (2)
Direct referral with urological symptoms (5)	Bladder (3) Colon (2)

Symptoms at the time of original presentation of the fistula arose from the urinary tract in seven patients, from the bowel and urinary tract in five and from the bowel in one patient. Diagnosis was confirmed in all cases by a combination of contrast studies of the lower bowel and urinary tract, computed tomography, cystoscopy and sigmoidoscopy.

All patients underwent surgery. One of the patients with cervical carcinoma had severe pelvic radiation damage and underwent a palliative urinary diversion since there was extensive tumour recurrence. All others underwent a potentially curative radical tumour resection (*Table 3*).

Results

Follow-up from the time of surgery ranged from 6 to 32 (median 13) months. Two patients died (nos 8 and 9), one after

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Table 3 *Details of diagnosis, operation and outcome in 13 patients*

Patient no.	Age (years)	Sex	Primary tumour	Primary procedure	Secondary procedure	Outcome
1	76	M	Bladder	Cystectomy and ileal loop, sigmoid colectomy		Well
2	78	M	Bladder	Total pelvic exenteration		Well
3	73	M	Bladder	Cystectomy and ileal loop, Hartmann's		Awaiting reversal of Hartmann's procedure
4	70	F	Bladder	Sigmoid colectomy, loop colostomy	Cystectomy, extended colectomy, ureteric reimplantation	Awaiting closure of colostomy
5	72	M	Colon	Total pelvic exenteration		Well
6	48	M	Colon	Partial cystectomy, sigmoid colectomy	Total pelvic exenteration, ileo-cystoplasty and colonic reconstruction	Recurrent fistula closed at tertiary procedure
7	74	M	Colon	Partial cystectomy, sigmoid colectomy	Resection of recurrent fistula and omental overlay	Well
8	61	M	Colon	Subtotal cystectomy, sigmoid colectomy and ileocaecocystoplasty		Died from distal metastases
9	70	F	Colon	Hartmann's	Partial cystectomy, sigmoid colectomy	Died from overwhelming sepsis
10	74	M	Colon	Partial cystectomy, Hartmann's		Recurrent fistula healed after transurethral resection of prostate
11	84	F	Colon	Partial cystectomy, sigmoid colectomy		Well
12	65	F	Cervix	Wertheim's hysterectomy	Urinary and faecal diversion	Well
13	46	F	Cervix	Anterior exenteration, ileal loop		Well

operation from overwhelming sepsis and one from metastatic disease 14 months after surgery. Both of these patients had been referred with local recurrence of colonic cancer in the bladder due to inadequate bladder resection. Other early postoperative complications included deep vein thrombosis (one case), chest infection (three cases) and pelvic abscess (one case). Excluding the patient who underwent palliative diversion, the other patients remain well with no signs of recurrent disease at the last review.

This selected group of patients presents a diverse range of surgical and management difficulties. These are discussed according to the specific problems encountered.

Resection of tumour and fistula

Complete excision of the tumour was achieved in all but one case, the patient with residual tumour having a combination of recurrent tumour and severe radiation damage (patient 12). Three of the patients had extensive local disease throughout the pelvis which required pelvic exenteration and permanent diversion of the urinary and intestinal tracts. Reconstruction was not attempted because of the extent of the tumour, the presence of postirradiation fibrosis, and the general condition and prognosis of the patients. Those patients in the series with transitional cell carcinoma of the bladder underwent radical cystectomy for local disease control, with continuity of the intestinal tract being restored primarily in one patient. Two are awaiting closure of defunctioning colostomies. The extent of colonic resection in these patients was determined by factors including the tumour size and spread, and the presence of any changes on radiotherapy. Twelve patients had the affected colonic segment resected. Of these, ten had continuity restored at the time of initial surgery, at a second procedure, or are awaiting colostomy closure. One of the patients (no. 4) had invasion of the lower part of the ureter causing obstruction and hydronephrosis which required local excision before anastomosis into an ileal conduit.

Reconstruction of the urinary and intestinal tracts

Patients in whom bladder resection resulted in a substantial reduction in capacity were considered for a reconstructive procedure. Substitution cystoplasty was performed in two patients. One underwent reconstruction with a hemi-Kock ileocystoplasty[11]. The technique incorporates a ureteric antireflux mechanism which consists of an intussuscepted nipple of ileum, held in position by three rows of TA55 (Auto Suture, Ascot, UK) staples. The other patient underwent a detubularized ileocaecal segment cystoplasty with prevention of reflux by ureteric implantation using the Leadbetter–Politano[12] method. Both techniques created a low pressure neobladder with a capacity greater than 400 ml. In each case the sphincter mechanisms were preserved, resulting in day- and night-time continence.

Reconstitution of the intestinal tract was performed in all patients except those undergoing total pelvic exenteration. This was not achieved in only one patient (no. 6).

Effects of external beam radiotherapy

Seven patients had previously undergone EBRT, including one with cervical carcinoma (patient 12) who had proved particularly sensitive to it, suffering radiation necrosis of the head of the femur and complex vesicovaginal and colovesical fistulae. The known healing problems in these patients dictated caution, with all colonic anastomoses being protected by a defunctioning colostomy or ileostomy for at least 2 months, and bladder suture lines by prolonged bladder drainage via a urethral catheter.

Formation of a defunctioning stoma

Intestinal stomas were fashioned in nine of the patients: as a permanent feature in three, as a temporary defunctioning procedure in four, and two patients await closure. In preference colonic stomas were fashioned from the sigmoid colon as end colostomies. One patient with a recurrent colovesical fistula had already undergone defunction with a sigmoid loop colostomy (patient 4). Unfortunately this led to a problem as urine drained from the distal lumen of the stoma and mixed with faeces from the proximal end, making stoma care extremely difficult. One patient (no. 6) underwent defunction with a loop ileostomy following sigmoid colectomy and ileocystoplasty.

Treatment of concurrent bladder outflow obstruction

Two male patients (nos 7 and 10) were referred with recurrence of a colovesical fistula which recurred following removal of the bladder catheter. Both patients had their outflow obstruction treated. In one patient a Hartmann's procedure had been performed and a cuff of bladder excised.

Discussion

Urinary tract complications of pelvic malignancy and their treatment remain a major challenge[13]. The prognosis in terms of life expectancy and quality of life following exenteration have improved[14] and continue to do so since the early results of Brunschwig and Barber[15]. If pelvic exenteration is not necessary the degree of surgical excision is determined by the site and histological origin of the primary tumour. Local resection of bladder invaded by colonic carcinoma must be wide. Too narrow a bladder resection margin in three patients in this series resulted in local recurrence within the bladder and two of these patients subsequently died from distant disease despite further surgical intervention.

If resection of the bladder substantially reduces overall capacity, consideration should be given to reconstructive procedures that restore intestinal continuity and provide adequate bladder capacity and continence. Conventional radical cystectomy and urinary diversion may lead to impairment of sexual function and the associated psychological and social implications of an incontinent abdominal stoma[16]. Nerve-sparing radical cystectomy and bladder reconstruction may restore bladder capacity and function by providing a high capacity, low pressure reservoir with preservation of a continent sphincter mechanism. Primary augmentation or substitution cystoplasty may be required, depending on the amount of bladder tissue resected. Various intestinal segments have been used, although terminal ileum alone[17] or in combination with the caecum[18] is most widely employed. Reconstructions of the urinary and intestinal tracts are best performed synchronously with interposition of the greater omentum if necessary to prevent recurrent fistula formation.

Pelvic tumours are often treated by EBRT, and colovesical fistulae in these patients may be due to tumour recurrence or radionecrosis[13,19]. Reconstructive surgery following EBRT is difficult owing to endarteritis[20] and a reduction in tissue compliance[21]. EBRT does not preclude reconstructive procedures provided that precautions are taken with prolonged protection of anastomoses. The anal and urethral sphincters are usually outside the field of radiation, and reconstruction should be feasible in the absence of local tumour infiltration[22], provided an assessment of sphincteric function is undertaken before operation.

Controversy remains over the choice between single-stage and multistage procedures for the treatment of uncomplicated colovesical fistulae[2,23]. The presence of previous EBRT, intestinal obstruction or abscess formation, concurrent reconstruction of the bladder, or an unprepared bowel dictate that the intestinal tract is defunctioned. Omental overlay may be an important adjunct to a successful outcome. A transverse colostomy may fix the omentum and make mobilization difficult or impossible. If extensive colonic resection is necessary, or in the presence of concurrent colonic pathology, a loop ileostomy should be considered[24].

Raised intravesical pressure should be avoided to protect bladder repair. In this series, two patients developed recurrent fistulae on removal of bladder drainage because of the development of raised intravesical pressure. When dealing with malignant fistulae consideration should be given to the extent of anatomical involvement of the urinary tract and the dynamics of urinary tract function before surgery. The principles of fistula surgery, excision of fistula track, sound closure of both epithelial surfaces and apposition of well vascularized tissue between them should be followed. Extensive pelvic surgery usually entails a multidisciplinary approach, with contributions from urologists, colorectal surgeons and gynaecologists. To obtain satisfactory patient survival rates, tumour excision should be aimed for, even if exenteration is necessary. Reconstruction of the urinary tract and the avoidance of stoma should be an objective but not at the expense of an increased perioperative mortality rate.

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Surgical workshop

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Laparoscopic fixation of sigmoid volvulus

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Colonic volvulus accounts for 1–2 per cent of cases of intestinal obstruction in western populations[1]. If conservative measures fail, colectomy is usually the treatment of choice. A case of laparoscopic fixation for a recurrent sigmoid volvulus is reported.

Surgical technique

A 75-year-old man was admitted with a 4-day history of abdominal colic, distension and constipation. Abdominal examination revealed gross distension and obstructed bowel sounds but no tenderness. Plain abdominal radiography showed a sigmoid volvulus and the gut was successfully decompressed using a rigid sigmoidoscope. The following day the distension recurred; the patient again underwent endoscopic decompression and a flatus tube was left *in situ*. On removal of this tube after 24 h the patient's symptoms and signs of obstruction recurred. In view of the patient's age and poor respiratory function laparoscopic fixation of the colon was performed.

Under general anaesthesia, pneumoperitoneum was established and a 10-mm cannula and telescope were introduced at the umbilicus. General inspection of the abdomen revealed a huge sigmoid loop with scarring at its base but no other abnormality. The rectosigmoid junction was identified and the colon was followed carefully with gasping forceps to a point under the right tenth rib. A 5-mm port was established there, and the colon was held at that point while the incision was increased to 3 cm to permit the colon to be brought up into the wound. Several silk seromuscular sutures were placed to fix the colon to the inner layer of the rectus sheath. The outer layer of the rectus sheath and skin were then closed and pneumoperitoneum was re-established.

The sigmoid loop was then followed from right to left under the transverse colon and a second point of fixation was fashioned in the left upper quadrant. Finally, a third point of fixation was established in the left iliac fossa. The end result is illustrated in *Figure 1*. The patient made an uncomplicated recovery and was discharged on the fourth day after operation. He has been followed up for 14 months, remains asymptomatic, and has had no further episodes of volvulus.

Discussion

There are several options if endoscopic measures fail to decompress a sigmoid volvulus or frequent recurrence becomes a problem. These include sigmoid resection with primary anastomosis, Hartmann's procedure, resection with exteriorization of both ends of colon and suture fixation sigmoidopexy.

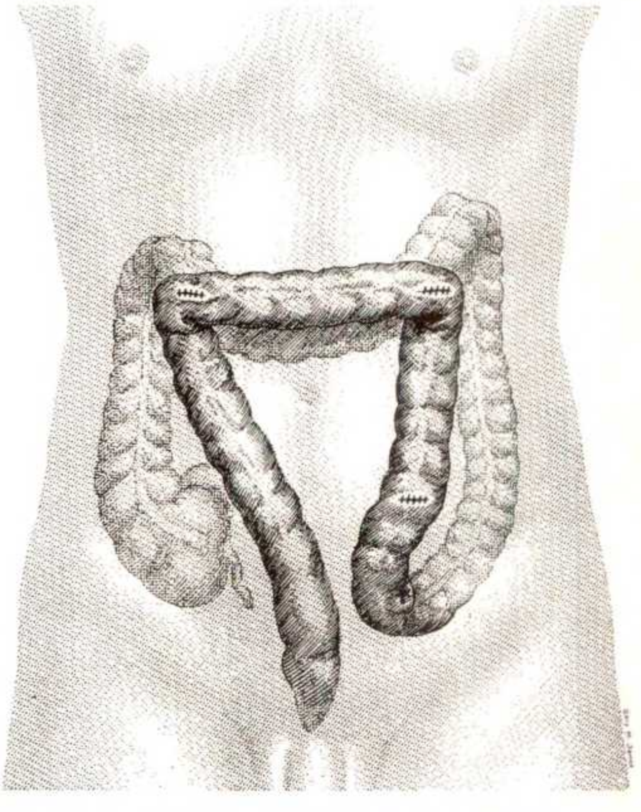

Figure 1 *Position of the colon following laparoscopic fixation*

The laparoscopic approach offers many advantages over laparotomy as it avoids the morbidity associated with a large abdominal wound. It was particularly suitable in the case presented as the patient was elderly and had poor lung function. These advantages must be weighed against the potential risk of recurrence, which is possibly less likely after resection than suture fixation.

In conclusion, it has been shown that laparoscopic fixation for sigmoid volvulus is a practical possibility and merits further evaluation, perhaps in the form of a randomized trial *versus* resection and primary anastomosis.

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Outcome in patients with early colorectal carcinoma

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Twenty-four patients seen between 1978 and 1990 with early colorectal carcinoma were reviewed to determine the outcome of surgical treatment. The mean age was 62 (range 35–79) years; there were 16 men and eight women. The site of the tumour was the ascending colon in two patients, sigmoid colon in ten and rectum in 12. The polypoid and flat–elevated ulcerated (IIa + IIc) subtypes were detected in 14 and nine lesions respectively. Restorative colectomy was carried out in 19 patients, and five required Miles' operation. There were no postoperative complications or deaths at a mean follow-up of 71 (range 12–151) months. Neither recurrence nor distant metastasis was found during follow-up. There was a close relationship between the depth of submucosal invasion and presence of flat–elevated ulcerated subtype lesions with lymphatic infiltration. This association may play an important role in the mechanism of metastasis. Major surgical resection is probably required if longer disease-free intervals and better cure rates are desired.

The incidence of colorectal cancer has increased and the disease remains a major source of morbidity and mortality. Progress in its control has been limited in the past 40 years[1–6]. The widespread use of endoscopy and the availability of mass screening[7,8] detects colorectal cancers at a rate comparable to that for stomach cancer, where early-stage cancers account for more than half of detected lesions[9]. Some surgeons adopt a more conservative attitude and remove most premalignant polyps or polyps containing invasive carcinoma endoscopically or by local excision[10–13]. The criteria for patient selection and the need for major surgical resection or adjuvant therapy are still debatable[12,14,15]. This study describes the outcome of patients with early colorectal cancer referred for surgical treatment.

Patients and methods

The records of 372 patients with colorectal carcinoma seen between 1978 and 1990 were reviewed. Twenty-four patients (6·5 per cent) had early-stage cancers (tumour invasion limited to the mucosal or submucosal layer by the criteria of the Japanese Research Society for Colon, Rectum and Anus[16]). The mean age of the 24 patients was 62 (range 35–79) years; 16 were men. The clinical findings at presentation and the type of operation performed were recorded. Patients who underwent endoscopic polypectomy only and those with inflammatory bowel disease and multiple polyposis were excluded. Lesions were classified endoscopically as follows: type I, polypoid (p, pedunculated; s, sessile); type II, superficial (flat–elevated, IIa subtype; flat–flat, IIb; flat–depressed, IIc; flat–elevated ulcerated, IIa + IIc); and type III, ulcerated (*Figure 1*)[16–18]. Preoperative assessment included measurement of the serum level of carcinoembryonic antigen (CEA), flexible endoscopy, barium enema, and computed tomography (CT) or magnetic resonance imaging (MRI). All patients had histopathological confirmation of colorectal carcinoma from preoperative biopsies and surgical specimens. The specimens and lymph nodes were fixed in formalin and cut into parallel 2-mm sections. Polypectomy specimens were cut into parallel 6-μm sections, 15 to 20 sections being examined. The depth of submucosal invasion was assessed and classified according to the criteria defined by Kudo *et al.*[19]. Three levels of invasion were defined: Sm_1, for invasion limited to the head of the polyp or the upper third of its stalk; Sm_2 and Sm_3, if the invasion reached the middle and lower third of the stalk, respectively; or considering sessile polyps, type II and III lesions (*Figure 2*). This scheme is similar to that of Haggitt *et al.* for colorectal adenomas containing invasive carcinomas[20]. The presence of invasion into vascular or lymphatic channels was evaluated and defined as follows: V_0 or Lym_0 if absent; V_{1-3} or Lym_{1-3} if mild, moderate or marked infiltration was noted. Tissue clearing optimized the detection of lymph node involvement and a minimum of three levels of sections per lymph node was examined by two pathologists.

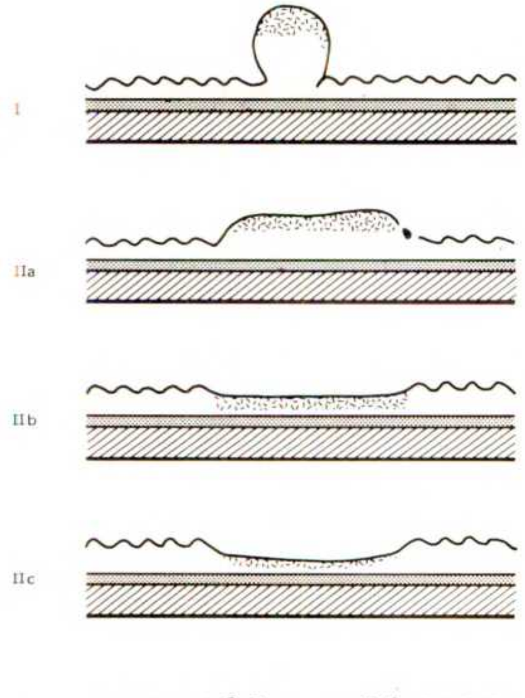

Figure 1 *The Japanese endoscopic classification for early colorectal cancer.* □, *Mucosa;* ▨, *submucosa;* ▨, *muscularis propria;* ■, *serosa*

Results

The most frequent finding at presentation (*Table 1*) was lower gastrointestinal bleeding (67 per cent of cases). Five patients were asymptomatic. No abnormal CEA levels were detected and no metastatic disease was seen on CT or MRI. Tumour site is shown in *Table 2*. The mean diameter of the lesions was 18 mm. Lesions <15 mm in diameter occurred in four patients; in 12 the lesion was 15–25 mm, and in eight >25 mm in size.

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The polypoid type (four pedunculated, ten sessile) was predominant, followed by the IIa + IIc subtype, which accounted for 14 and nine lesions respectively (*Table 2*). No synchronous colorectal tumours were detected. The eight mucosal cancers were excised rather than removed by endoscopic polypectomy because the lesions were large sessile polyps (four sigmoid, two rectal), a pedunculated tumour with involved polypectomy margins, and one large adenoma containing carcinoma in the lower rectum. Two patients underwent local excision owing to advanced age and another because of severe heart disease. There were no postoperative complications or deaths. Histological examination revealed a well differentiated adenocarcinoma in all mucosal lesions and in 11 instances of submucosal invasion. The remaining five submucosal lesions were moderately differentiated adenocarcinomas. The depth of submucosal invasion and its relationship to the type of tumour and vascular infiltration are demonstrated in *Table 3*. Of the 16 patients with tumour extending into the submucosa, unequivocal vascular infiltration was identified in four (Lym_3V_3). In four others there was lymphatic (Lym_3V_0) or venous (Lym_0V_{2-3}) infiltration. All these lesions were >25 mm in diameter and/or Sm_2 or Sm_3 degree of submucosal invasion. In all but one patient (Lym_3V_0) no lymph node metastases were seen. The follow-up ranged from 12 to 151 (mean 71) months. Three patients died from causes unrelated to the cancer; two of advanced age and another from severe heart disease. Neither recurrence nor distant metastasis was detected during a follow-up of at least 1 year.

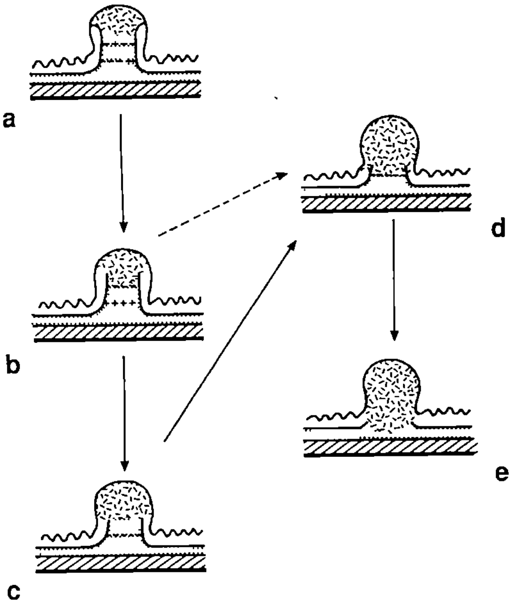

Figure 2 *The histological classification of depth of invasion into the submucosa.* **a–c** *Sm_1;* **d** *Sm_2,* **e** *Sm_3. □, Mucosa, ⬚, submucosa; ▨, muscularis propria, ■, serosa*

Table 1 *Clinical findings at presentation*

Finding*	*n*
Rectal bleeding or positive occult blood test	16
Altered (slender or mucous) faeces	6
Change in bowel movements (diarrhoea or constipation)	4
Asymptomatic	5

*Some patients had more than one feature

Discussion

Endoscopic therapy is the preferred method of treatment, especially for adenomas containing carcinoma, mucosal and some submucosal cancers. Most of the lesions are polypoid or located in the lower rectum and allow easy endoscopic removal or local excision[10–13]. Kudo *et al.*[19] addressed the depth of submucosal invasion as a risk factor and 20 and 25 per cent of patients had vascular and lymph node infiltration, respectively, when the invasion extended deeply into the submucosa. In this series half of the patients with Sm_{1-3} tumours had vascular infiltration; this showed a close relationship with the depth of invasion – most cases of Sm_3 invasion had both lymphatic and venous infiltration. Similar results concerning submucosal invasion have been reported by Nivatvongs *et al*[15]. Subtype IIa + IIc tumours show an increased percentage of vascular infiltration[13,21]. Six of eight patients showed marked lymphatic or venous invasion and one instance of IIa + IIc subtype with Sm_{1c} level invasion had lymph node involvement. This patient had a low rectal tumour (26 mm) and underwent Miles' operation. Hara *et al.*[11], in a series of ten patients with submucosal cancer, found two instances of recurrence in three patients undergoing polypectomy (three sessile polyps), and one patient with lymph node and hepatic metastasis. These patients had lymphatic and massive submucosal invasion.

Table 3 *Depth of invasion into submucosa and vessel infiltration*

Depth of invasion		Type				Total with infiltration
		Ip	Is	IIa + IIc	III	
Sm_1	a				○	0
	b	○○		○		0
	c			◐*		1
Sm_2			○○○	○◑◑		2
Sm_3		●	●	◐●◑		5
Total with infiltration		1	1	6	0	8

○, Absence of lymphatic and vein invasion; ◐, positive lymphatic invasion; ◑, positive vein invasion, ●, positive lymphatic and vein invasion, *patient with positive paracolic lymph node

Table 2 *Site and type of early colorectal carcinomas*

Type	Depth of invasion		Colon (*n* = 12)				Rectum (*n* = 12)						Total
			Ascending		Sigmoid		Upper		Middle		Lower		
	M	Sm	M	Sm	M	Sm	M	Sm	M	Sm	M	Sm	
Ip	1	3	0	1	1	2	0	0	0	0	0	0	4
Is	6	4	0	0	3	1	0	0	1	1	2	2	10
IIa + IIc	1	8	0	1	0	2	0	1	0	2	1	2	9
III	0	1	0	0	0	1	0	0	0	0	0	0	1
Total	8	16	0	2	4	6	0	1	1	3	3	4	24

M, mucosa only; Sm, mucosal and submucosal layer

Matsuda *et al.*[21] reported one instance of lymph node involvement and two other patients with residual tumour after polypectomy in a series of 15 patients, of whom 13 had massive submucosal invasion. Tumours limited to the mucosal layer usually have no lymph node involvement or distant metastases[22–24] Once submucosal invasion has occurred there is an increased risk of metastasis, perhaps by the time of initial treatment[10,11,24] In this series, in all four patients who had previously undergone polypectomy the polypectomy margins were involved with neoplastic cells, and in two patients massive submucosal invasion was found. It is difficult to define the depth of invasion on polypectomy specimens compared with resected specimens and in this situation the presence of moderate to marked lymphatic and venous infiltration might be better criteria for further surgical treatment. Colonic resection and colostomy was performed in five patients It has been demonstrated that cure rates in sphincter-preserving procedures are comparable to those for abdominoperineal resection[5,25–28] Good results of local excision for low-lying early rectal carcinomas have been reported[12,13]. The patients who underwent low anterior resection and local excision (seven cases) remain disease-free 3–8 years after surgery The number of patients in this and previous[11,13,21] studies is small for firm conclusions to be drawn. Massive submucosal invasion and IIa + IIc lesions may play an important role in the mechanism of dissemination, leading immediately to lymphatic infiltration, since a significant association was found between submucosal invasion and the presence of IIa + IIc lesions with lymphatic infiltration. Further investigations are needed to clarify this mechanism and to assess the true risk for lymph node metastasis. If a minor procedure is to be performed then radiation therapy (associated with favourable results[29–31]) and close follow-up may be necessary.

Submucosal invasion from Sm_{1c} level to massive invasion (Sm_3) when associated with flat-elevated ulcerated (IIa + IIc) subtype lesions are determinant factors for lymphatic infiltration and possible tumour dissemination Removal of the tumour site containing the regional lymph nodes should be carried out because of the possibility of lymph node metastasis and tumour progression.

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Restoration of continence following rectopexy for rectal prolapse and recovery of the internal anal sphincter electromyogram

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Twenty-two patients with full-thickness rectal prolapse underwent ambulatory fine wire electromyography of the internal anal sphincter (IAS), external anal sphincter and puborectalis, together with anorectal manometry, using a computerized system. Examinations were performed both before and 3 to 4 months after rectopexy. The median (interquartile range (i.q.r.)) preoperative IAS electromyogram (EMG) frequency was 0·18 (0·05–0·31) Hz and the median (i.q.r.) preoperative resting anal pressure was 28 (15–64) cmH$_2$O. An improvement in the IAS EMG frequency, median (i.q.r.) 0·29 (0·19–0·38) Hz ($P < 0\cdot03$)*, and resting anal pressure, median (i.q.r.) 41 (20–72) cmH$_2$O* ($P < 0\cdot05$)*, was recorded after operation, but these variables remained significantly lower than those found in normal controls: median (i.q.r.) IAS EMG frequency 0·44 (0·36–0·48) Hz and median (i.q.r.) resting anal pressure 92 (74–98) cmH$_2$O. We suggest that repair of the prolapse allows the IAS to recover by removing the cause of persistent rectoanal inhibition.*

Full-thickness rectal prolapse is accompanied by faecal incontinence in approximately 75 per cent of patients. Rectopexy is usually successful in correcting the prolapse and cures the associated faecal incontinence in 80–90 per cent of patients[1,2]. We propose that prolapse causes reversible rectoanal inhibition, and suggest that restoration of continence following rectopexy is associated with removal of this inhibition. To investigate this hypothesis, a group of patients with full-thickness rectal prolapse has been studied prospectively before and after rectopexy using a computerized ambulatory monitoring system.

Patients and methods

Twenty-two patients (20 women) with complete rectal prolapse and faecal incontinence and a control group of 17 normal subjects (ten women) were studied. The median (range) age was 78 (37–88) years in patients and 31 (25–74) years in controls.

Fine wire electromyography was performed using barbed and bared polytetrafluoroethylene-coated stainless steel wires (0·13 mm diameter); the internal anal sphincter (IAS), external anal sphincter and puborectalis muscle were examined. The patient was placed in the left lateral position and an intradermal bleb of 0·5 per cent lignocaine was infiltrated into the anal verge using a 21 Fr needle before introduction of the wires. These were attached and connected to a portable amplifier contained within the ambulatory recorder (Gaeltec, Isle of Skye, UK). Anorectal manometry was simultaneously performed using four microtransducers contained in a probe of 3 mm diameter. The pressure transducers were located at 2 and 6 cm, with two 12 cm from the tip of the probe. The pressure recorder was connected by an adaptor to the ambulatory recorder to allow for integrated electromyogram (EMG) and pressure recordings.

The rectoanal inhibitory reflex was obtained using a latex balloon securely mounted on a 14 Fr Nelaton catheter (Mediplast, Salna, Sweden) which was in turn connected by a three-way tap to a 50-ml Luer-Lok syringe. The latex balloon was inserted into the rectum 8 cm from the anal verge and inflated with increasing volumes of air. Rectoanal inhibition of >10 cmH$_2$O below resting pressure lasting 1 min was defined as a positive reflex.

The patient was then discharged from hospital, and kept a diary of passage of flatus, defaecation and micturition. After completion of the recording, the information stored on the ambulatory recorder was off-loaded on to a computer (Archimedes Taxan 410; Acorn, Cambridge, UK) to give a permanent record for subsequent analysis.

Each patient with a complete rectal prolapse and each control underwent ambulatory monitoring for a median (range) of 8 (2–16) h. Patients also underwent ambulatory recordings 3–4 months after rectopexy for a median (range) of 2·1 (1–5) h.

Resection rectopexy was performed on each patient with rectal prolapse. This involved complete posterior mobilization of the rectum with division of the lateral ligaments. The splenic flexure and left colon were mobilized and the redundancy resected. The descending colon was then anastomosed to the rectum 12 cm from the anal margin, before anastomosis the rectum was tethered to the presacral fascia with 2/0 polypropylene sutures, which were tied on completion of the anastomosis.

Comparisons between controls and subjects were made using the Mann–Whitney *U* test and those between preoperative and postoperative findings using the Wilcoxon rank sum test.

Results

The IAS EMG frequencies and resting anal pressures were examined by two different observers. There was no significant interobserver variation.

There was no correlation in the control group between the age of the subjects and IAS EMG frequency ($r_S = -0\cdot34$, $P = 0\cdot19$) or between the age of subjects and resting anal pressures ($r_S = -0\cdot37$, $P = 0\cdot14$). No significant sex-related differences were noted in this group for median (interquartile range (i.q.r.)) IAS EMG frequency: men 0·44 (0·38–0·46) Hz; women 0·44 (0·30–0·49) Hz ($P > 0\cdot1$). Furthermore, there was no statistically significant difference in resting median (i.q.r.) anal pressures between men and women (men 95 (77–101) cmH$_2$O; women 90 (72–99) cmH$_2$O ($P > 0\cdot1$)). Having ascertained this, the whole control group was used for comparison.

Internal sphincter electromyogram frequency

The median (i.q.r.) preoperative IAS EMG frequency for patients was 0·18 (0·05–0·31) Hz and for controls 0·44 (0·36–0·48) Hz ($P < 0\cdot01$). The median (i.q.r.) postoperative IAS EMG frequency was 0·29 (0·19–0·38) Hz. This was significantly improved compared with the IAS EMG before rectopexy ($P < 0\cdot03$) but was still significantly different from that of the control group ($P < 0\cdot01$) (*Figure 1*).

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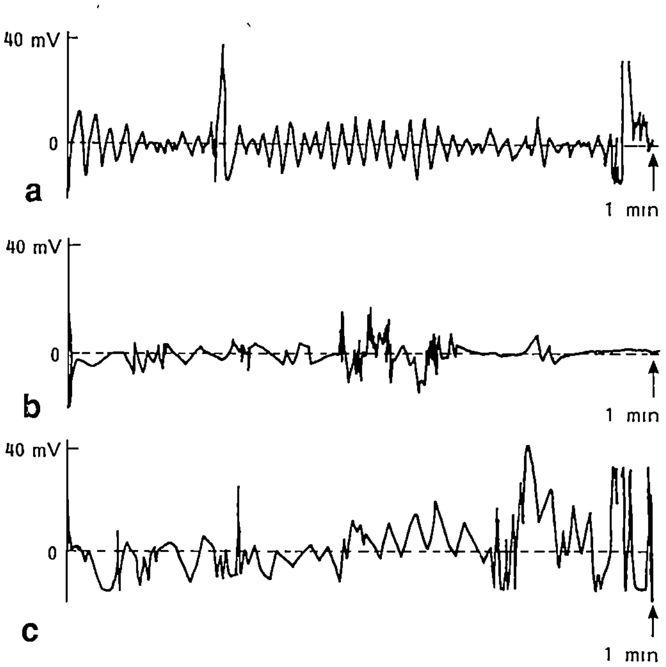

Figure 1 *Electromyography of the internal anal sphincter* **a** *in a normal control,* **b** *before and* **c** *after rectopexy in a patient with full-thickness rectal prolapse*

Basal pressures

The median (i.q.r.) resting anal pressure before rectopexy was 28 (15–64) cmH$_2$O while the median (i.q.r.) resting anal pressure of the control group was 92 (74–98) cmH$_2$O ($P < 0{\cdot}001$).

The median (i.q.r.) postoperative resting anal pressure showed a recovery to 41 (20–72) cmH$_2$O ($P < 0{\cdot}05$), although this variable also remained significantly lower than that of the control group ($P < 0{\cdot}01$).

Maximum voluntary squeeze pressures

The median (i.q.r.) preoperative squeeze pressure was 54 (48–65) cmH$_2$O compared with a median (i.q.r.) postoperative squeeze pressure of 61 (48–79) cmH$_2$O ($P > 0{\cdot}1$). Patient squeeze pressures before and after surgery were significantly lower than the squeeze pressures of the control group; the median (i.q.r.) for controls was 256 (188–374) cmH$_2$O ($P < 0{\cdot}001$).

Rectoanal inhibitory reflex

The presence of the rectoanal inhibitory reflex was documented before and after rectopexy. This reflex was absent in 16 patients before operation and returned in all cases when measured after operation. The volume of air required to elicit this reflex after surgery, however, was much larger than that required for controls (patient range 90–300 ml compared with a control range of 40–55 ml).

The grade of continence[3] was compared before and after surgery using the χ^2 test. Continence was significantly improved (continent to solid and liquid stool) in all but one patient who underwent resection rectopexy ($P < 0{\cdot}005$). This patient had almost recovered continence at 6-month review, but still experienced minor episodes of soiling.

Discussion

Abdominal procedures appear to be more successful than perineal ones for restoring continence[4]. The factors which contribute to restoration of continence following such surgery have been debated previously[5–8] Constipation after operation was considered by some to have accounted for the restoration of continence as it occurred in 47 per cent of patients following Ivalon sponge (Downs Surgical, Sheffield, UK) rectopexy[5]. Recovery of the IAS has been suggested as an alternative explanation[6,7,9].

Relatively long recordings were obtained before operation in the present study to allow evaluation of episodes of transient IAS relaxation, and events such as passage of flatus, defaecation and micturition. These events provide important information concerning the mechanism of faecal incontinence and cannot be adequately assessed by orthodox laboratory-based techniques. It is our experience that a minimum recording of 1 h is required when assessing ambulatory anal pressures, as these rise significantly from the typical values obtained in the laboratory[2].

The recordings after operation were significantly shorter as the primary aim was to measure the IAS EMG frequency and resting anal pressures for a minimum of 1 h. Unlike resting anal pressures, the IAS EMG frequency does not change significantly in the ambulatory setting.

It is difficult to demonstrate the rectoanal reflex in patients with rectal prolapse who have low pressures, since the IAS is already maximally inhibited in most of those with prolapse and incontinence. Nevertheless, after operation it was possible to demonstrate a recovery of the rectoanal inhibitory reflex for 1 min in 16 patients, although large volumes were required to elicit the reflex. Spencer[6] has suggested that rectal prolapse results in rectoanal inhibition and that this, together with abnormal anorectal sensation, is an important aetiological factor in the pathogenesis of incontinence. The present findings support this hypothesis as the IAS EMG appears to be electrically 'switched off' in patients with prolapse. This EMG inactivity is demonstrably reversible as there is a recovery of electrical activity following rectopexy.

It would appear that such recovery is not fully complete, as after surgery both the IAS EMG frequencies and resting anal pressures of the patients were significantly lower than those of controls. An increase in maximum squeeze pressure was also recorded after operation, but this was not statistically significant. The finding that resting anal pressure increases after operation is in agreement with other series[6,7,9].

One of the reasons for improvement of continence following rectopexy is IAS recovery. It has also been shown that anorectal sensation improves after surgery[10]. Improvement of anal sphincter function and anorectal sensation after rectopexy contribute to restoration of continence.

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Surgical Research Society Abstracts

Br. J. Surg. 1992, Vol. 79, May,
A441–A468

The following abstracts were presented at the 75th meeting of the Surgical Research Society, with Professor N. Browse in the chair. The meeting was held on 9–10 January 1992 at The Royal College of Surgeons of England and was organized by the Academic Surgical Unit at St Mary's Hospital. One hundred and nine papers were presented during the Scientific sessions, which were preceded by a symposium entitled 'Adjuvant therapy for cancer'. The Patey Prize was awarded to Ms S. Homer-Vanniasinkam for her paper entitled 'Modulation of lipid mediators in the prevention of muscle infarction and oedema during reperfusion after ischaemia'.

Postoperative neutrophil activation: an early marker of the sepsis response

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Previous studies of polymorphonuclear leucocytes (PMNLs) have suggested that major surgery induces postoperative PMNL dysfunction. In contrast, it is now considered that the injury associated with severe sepsis and multiorgan failure is determined by the degree of host response (leucocyte activation) rather than the severity of the infection itself. The aim of the present study was to determine whether there was any relationship between postoperative changes of PMNL activation and the development of postoperative sepsis. Using flow cytometry, functional (hydrogen peroxide (H_2O_2) production) and phenotypic (adhesion/complement receptor, CD11b) markers of PMNL activation were studied in 28 patients undergoing elective resectional surgery, 11 of whom developed postoperative infections more than 5 days after surgery. Data are expressed as mean(s.e.m.) channel fluorescence for each parameter, before operation and on day 1 after operation.

	H_2O_2 production		CD11b expression	
	Preop.	Day 1	Preop	Day 1
No complications	109·15(4·91)	109·61(3·05)	97·8(6·2)	128·6(8·1)
Sepsis	104·53(6·23)	120·43(2·56)	101·41(7·9)	192·5(38·0)

Both H_2O_2 production and CD11b expression were increased within 24 h of surgery in the group who subsequently developed sepsis ($P < 0{\cdot}05$, Student's paired t test). Although the two groups were clinically indistinguishable on day 1, CD11b expression and H_2O_2 production were significantly greater in PMNLs from the complicated than from the uncomplicated group ($P < 0{\cdot}05$ and $P < 0{\cdot}0001$, respectively, ANOVA). We suggest that an exaggerated PMNL activation response to surgery is an early event in patients destined to develop postoperative infection.

Comparison between gastric intramucosal pH and pulmonary artery oxygen transport measurements on the intensive care unit

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Of deaths on a surgical intensive care unit, 85 per cent are from multiple organ failure, and it is probable that splanchnic mucosal ischaemia plays a major pathogenic role. Current methods of assessing adequate perfusion and oxygenation of the tissues rely on global measurements of oxygen delivery and consumption by the Swan–Ganz pulmonary artery catheter, but one cannot relate these to specific regional circulations, in particular the splanchnic circulation. It is now possible to measure the intramucosal pH (pH_i) of the gastrointestinal tract indirectly with a tonometer, thus providing an indication of whether the gastrointestinal mucosa is being adequately oxygenated. This study was set up to compare the predictive value of tonometry with that of the more invasive measurements of global oxygen delivery and consumption.

In 83 patients studied, there were significant differences in mean pH_i between survivors and non-survivors on admission and 12 and 24 h after admission. In patients who had normal pH_i on admission and at 24 h there was a mortality rate of 11 per cent, but in those with a low pH_i on admission and 24 h later, there was a mortality rate of 80 per cent. Conversely, there were no significant differences in oxygen delivery and consumption between survivors and non-survivors (mean oxygen delivery at 24 h 667 ml min^{-1} m^{-2} for survivors and 588 ml min^{-1} m^{-2} for non-survivors; mean oxygen consumption at 24 h 127 ml min^{-1} m^{-2} for survivors and 133 ml min^{-1} m^{-2} for non-survivors). Furthermore, measurements of D_{O_2} and V_{O_2} in the first 24 h had no predictive value for outcome. Thus, intramucosal acidosis correlated with mortality rates far more closely than did poor oxygen transport, suggesting that splanchnic ischaemia is an important contributor to morbidity and mortality on the intensive care unit. This opens up numerous possibilities for therapeutic intervention and improvement of outcome.

Randomized controlled trial of loop ileostomy in restorative proctocolectomy

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A randomized controlled trial has assessed the role of loop ileostomy (LI) in totally stapled restorative proctocolectomy (RPC). Entry criteria included all patients who were not receiving steroids and where on-table testing revealed a watertight pouch with intact ileoanal anastomosis. Of 59 patients undergoing RPC over a 36-month period, 45 were eligible for the trial (23 LI, 22 no LI).

The two groups were comparable for age and diagnosis. Median operating time was 160 min for RPC and LI and 45 min for LI closure, compared with 150 min for RPC without LI. There were no deaths. Twelve patients developed LI complications (five flux, three retraction, one fistula, two hernias, three bowel obstruction). Two ileoanal anastomotic leaks occurred, one in each group. The unprotected patient required proximal diversion and repair. Ileoanal stenosis occurred in five patients with and one without LI. One patient with LI developed pouch torsion necessitating pouch excision. The incidence of sepsis, obstruction and pouchitis was similar. Total hospital stay was 23 (range 13–75) days with LI *versus* 13 (range 7–119) days without ($P < 0{\cdot}01$, Wilcoxon test).

This study indicated a low risk of pelvic sepsis which was not increased by avoiding a protective ileostomy. Furthermore, LI carried its own high incidence of complications.

Reperfusion plasma and microvascular injury

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The reperfusion of ischaemic tissue during aortic aneurysm repair results in the production of inflammatory mediators and neutrophil activation, and is complicated by remote lung injury. The aim of this study was to test the ability of human reperfusion plasma to create a remote microvascular injury using an *in vivo* chemotactic model. Vena caval blood was obtained from 12 patients undergoing aortic aneurysm

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repair 15 min after clamp removal and from ten patients undergoing laparotomy. Plasma was introduced into unit dose blister chambers fixed atop of dermabrasions on the back of depilated rabbits. After 3 h neutrophil counts and activity (free radical production by flow cytometry), protein accumulation and inflammatory mediators (thromboxane) were measured.

	Neutrophil accumulation at 3 h (per mm^3)	Neutrophil activity at 3 h (MFU)	Protein (μg ml^{-1})		Thromboxane (pg ml^{-1})	
			0 h	3 h	0 h	3 h
Aortic plasma	1636(210)*	276(31)*	94(23)	554(90)*	396(97)*	1090(105)*
Control plasma	63(25)	135(11)	101(31)	324(41)	143(61)	344(72)
Saline	36(19)	71(9)	0	217(46)	0	136(43)

MFU, mean fluorescence units. *$P < 0·01$ *versus* control plasma (ANOVA)

Reperfusion plasma produced a microvascular injury characterized by thromboxane production, neutrophil accumulation and activation, and increased microvascular permeability to protein.

Acid clearance in gastro-oesophageal reflux disease: studies in ambulatory subjects

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Patients with gastro-oesophageal reflux disease are said to have an impaired ability to clear refluxed acid. Most methods for assessing acid clearance are indirect measurements made on fasted, immobile subjects studied over a short period of time. Results may bear little relationship to normal ambulant conditions.

To study patients under more physiological conditions, a fully portable system has been developed. It consists of a pH electrode, a manometry catheter (containing three oesophageal–body transducers, a sphincter-sensing device and a gastric transducer), a 24-h recording box and software for automated waveform analysis. Ten patients with erosive oesophagitis were studied and compared with ten asymptomatic subjects. Reflux episodes were examined for different acid clearance patterns.

Median (interquartile range) lower oesophageal sphincter pressure was slightly lower in patients than in controls (9 (3–10) *versus* 14·5 (7–19) mmHg, P not significant). Patients with oesophagitis had a greater number of reflux episodes (39 (22–46) *versus* 10 (5·5–19); $P < 0·01$, Wilcoxon test) and a greater percentage of time at pH < 4 (18·2 (7·2–23) *versus* 0·9 (0·15–1·5) per cent, $P < 0·01$, Wilcoxon test). They had a longer time to the first peristaltic contractions (87 (67–132) *versus* 41 (23–60) s, $P < 0·05$, Wilcoxon test) and longer intervals between peristaltic contractions (132 (99–154) *versus* 56 (46–67) s; $P < 0·01$, Wilcoxon test) during reflux episodes. In all ten oesophagitis patients, long reflux periods were characterized by further reflux events before complete acid clearance.

Patients with oesophagitis have been shown for the first time to demonstrate a decreased ability to clear refluxed acid during long-term ambulatory studies. A number of mechanisms appear to be involved in this phenomenon.

Effect of arginine on natural cytotoxicity in cancer patients and healthy volunteers

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The amino acid L-arginine has antitumour effects in experimental animals, which are thought to be due to an immune stimulatory effect. In humans, arginine enhances lymphocyte transformation. It has been documented that arginine enhanced natural cytotoxicity in volunteers. Arginine significantly increased the number of peripheral blood lymphocytes (PBLs) which were phenotypically natural killer (NK) cells (CD56$^+$) and increased NK and lymphokine-activated killer (LAK) cell cytotoxicity[1].

Natural cytotoxicity is important in host anticancer defences, and therefore the effect of dietary arginine (30 g day^{-1} for 3 days) on lymphocyte phenotypes and NK and LAK cell cytotoxicity in the peripheral blood of 16 breast cancer patients (17 cancers. T_1, $n = 4$; T_3, $n = 9$; T_4, $n = 4$) was assessed.

In breast cancer patients there was a trend towards an increase in the number of circulating CD56$^+$ cells and significant increases in NK and LAK cell cytotoxicity (mean increases of 81 and 107 per cent respectively, $P < 0·001$, Student's paired t test). Effects of repeated doses of arginine were assessed in six patients, with locally advanced tumours, undergoing four cycles of neoadjuvant chemotherapy at 3-week intervals. Arginine 30 g day^{-1} for 3 days was given before each cycle of chemotherapy. In each cycle there was a significant increase in NK cytotoxicity following arginine ($P < 0·05$, Student's paired t test), demonstrating that enhanced cytotoxicity occurs on repeated administration of arginine.

To determine whether interleukin 2 (IL-2) was involved in the arginine-enhanced cytotoxicity in breast cancer patients, IL-2 PBL receptor expression (CD25) and *in vivo* serum IL-2 levels were measured, before and following 3 days of arginine. There was no significant change in CD25 expression but arginine tended to increase levels of IL-2 (*in vivo*) following arginine ($P = 0·065$). These results suggest that arginine may enhance natural cytotoxicity by increasing IL-2 production.

These are the first documented results revealing a stimulatory effect of L-arginine on human natural cytotoxicity in patients with breast cancer. Arginine may therefore have a role as an immune biological modifier in cancer treatment.

1 Park KGM, Hayes PD, Garlick PJ, Sewell H, Eremin O. Stimulation of lymphocyte natural cytotoxicity by L-arginine. *Lancet* 1991; **337**: 645–6

Modulation of lipid mediators in the prevention of muscle infarction and oedema during reperfusion after ischaemia

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Reperfusion injury complicating surgery for acute limb ischaemia may lead to amputation. Lipid peroxidation of endothelial and neutrophil cell membranes may promote this injury, although it is unclear which of the released lipid mediators is important. Although prostanoid synthesis should be beneficial, that of thromboxane (Tx) and leukotrienes may not be so (vasoconstriction, platelet activation, neutrophil chemotaxis, vasopermeability). Thus, in a rat model of 6 h unilateral hindlimb ischaemia and 4 h reperfusion, intravenous infusions (4·5 h) of a lipid peroxidation inhibitor (U74500A, 2 mg kg^{-1} 4·5 h^{-1}) and specific receptor antagonists (RA) to TxA_2 (GR32191, 10 μg kg^{-1} min^{-1}) and LTB_4 (SC41930, 1 mg kg^{-1} 4·5 h^{-1}) were given from 30 min before reperfusion, after which indices of muscle oedema (wet:dry weight) and muscle viability (nitroblue tetrazolium, histochemical staining) were calculated (reperfused:contralateral limb). These were compared with those in normal, ischaemic (tourniquet *in situ*) and control (no infusion) rats.

Group	n	Viability index	Oedema index
Normal	10	1·00 (1·00–1·00)	1·00 (0·98–1·01)
Ischaemic	12	1·00 (1·00–1·00)	1·01 (0·99–1·03)
Control	12	0·53 (0·33–0·61)	1·23 (1·09–1·37)
TxA_2	6	1·00 (0·70–1·00)	1·31 (1·23–1·38)
LTB_4	12	1·00 (1·00–1·00)	1·08 (1·05–1·10)
U74500A	9	1·00 (1·00–1·00)	1·33 (1·00–1·37)

Values are median (interquartile range)

Ischaemia lasting 6 h caused neither muscle infarction nor oedema (P not significant *versus* normal), but ischaemia with reperfusion resulted in both ($P < 0·01$, control *versus* normal or ischaemic). The LTB_4 RA prevented these changes ($P < 0·01$ *versus* control, P not significant *versus* normal). Muscle death was also prevented by U74500A and reduced by the TxA_2 RA (both $P < 0·01$ *versus* control, P not significant *versus* normal), but reperfusion oedema still occurred (TxA_2 RA, $P < 0·01$ *versus* normal; U74500A, $P < 0·05$ *versus* normal). Thus LTB_4 (neutrophil chemotaxis, chemokinesis, activator) is an important mediator of muscle necrosis and oedema during reperfusion, affirming a major role for neutrophils. Moreover, both LTB_4 RA and U74500A may have an adjuvant role in the therapy of acute limb ischaemia.

Inhibitory influence of analogues of somatostatin and bombesin on colonic cancer xenografts in nude mice

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Somatostatin and gastrin-releasing peptide (a mammalian homologue of amphibian bombesin) regulate production of gastrointestinal hormones and growth factors thought to exert trophic influences in colonic neoplasia.

The aim of this study was to assess the inhibitory effects in nude mice of RC-160 (somatostatin agonist) and RC-3095 (bombesin antagonist) on xenografts of the human colonic cancer cell line HT29.

Tumour xenografts were established in groups ($n = 10$) of nude mice by subcutaneous flank injection. Peptides (RC-3095 20 μg day^{-1} or depot RC-160 microcapsules releasing 50 μg day^{-1}) were injected after 2 weeks for a treatment period of 4 weeks. Tumour volume, burden (milligrams tumour per gram body-weight) and growth delay (time taken to reach tumour volume of 300 mm^3) were calculated from twice-weekly caliper measurements. The animals were killed after 28 days of treatment, and serum was collected for gastrin and insulin-like growth factor 1 (IGF-1) levels. Results were expressed as mean(s.e.m.) and compared with those of saline-injected controls.

RC-160 produced significant inhibition of tumour volume compared with controls at day 24 (290·9(61·1) *versus* 595·9(99·2) mm^3, $P < 0·03$), but by day 28 no significant difference in tumour volume was apparent. Serum gastrin and IGF-1 levels were also unaltered. By contrast, RC-3095 significantly inhibited growth by day 21 ($P = 0·01$), which persisted to day 28 (309·7(108·8) *versus* 681·8(101·5) mm^3, $P < 0·01$). Significantly decreased tumour burden ($P < 0·01$) and increased tumour growth delay (8·5 days longer than in controls) were observed in this group. Serum gastrin and IGF-1 levels were decreased to 72 per cent ($P < 0·05$) and 48 per cent ($P < 0·05$) of control values, respectively.

The growth inhibitory effect of RC-160 was short lived, whereas that of RC-3095 was markedly superior and sustained. A close correlation between growth inhibition and decreased IGF-1 levels was observed. RC-3095 warrants further evaluation in the treatment of advanced colonic cancer.

Mechanism of neutrophil adhesion to reperfused endothelium

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Reperfusion injury occurs when endothelium undergoes transient hypoxia in the presence of neutrophils. It requires an interaction between neutrophil adherence receptors (CD18) and endothelial cell ligands (intercellular adhesion molecule 1 (ICAM-1)). In these experiments, the nature of hypoxic injury to isolated endothelium and the response to cytokine stimulation are elucidated.

Umbilical vein endothelial cells were subjected, with or without cytokine (tumour necrosis factor (TNF)) coincubation, to 4 h of hypoxia and 50 min reperfusion. Neutrophils, with or without incubation in anti-CD18, were then added for 10 min and adherence was measured by myeloperoxidase assay. ICAM-1 assays were performed by staining with ICAM-1 antibodies. Controls were not subjected to hypoxia.

	Neutrophil adhesion (× 10^3)			
	No TNF	No TNF/CD18	TNF	TNF/CD18 antibody
Controls	8·5(1·1)	−0·3(0·6)	63·5(2·0)	22·0(1·4)
Hypoxia	12·4(1·0)*	0·9(0·5)†	52·6(2·5)*	8·8(1·1)*

Values are mean(s.e.m.) *$P < 0·01$ *versus* controls, †P not significant *versus* controls (Mann–Whitney U test and Student's t test)

TNF stimulation increased ICAM-1 on controls to 1·66(0·11), but neither hypoxia alone nor stimulation affected ICAM-1 on reperfused cells (0·92(0·20), $P < 0·05$).

With or without cytokine stimulation, reperfused endothelium demonstrates CD18-dependent increased neutrophil adhesion, without up-regulation of ICAM-1, which was previously thought to be a prerequisite for this interaction.

Prostacyclin production by endothelial seeded angioplasty sites

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Percutaneous transluminal angioplasty (PTA) of atheromatous lesions produces endothelial desquamation, activation of blood constituents, and platelet deposition. It is postulated that endothelial seeding of angioplasty sites may increase local prostacyclin production, reduce platelet deposition, and therefore reduce restenosis rates.

An *in vitro* model has been developed to facilitate study of endothelial seeding of angioplasty sites. Balloon dilatation of segments of long saphenous vein produces endothelial desquamation, splitting of the internal elastic lamina, and exposure of subendothelial collagen; these are changes similar to those seen after PTA of atheromatous lesions.

Punch biopsies of dilated saphenous vein 5 mm in size were seeded for 30 min at an approximate density of 5 × 10^6 human umbilical vein endothelial cells per cm^2. Basal and thrombin-stimulated prostacyclin release were assayed in control, dilated and seeded veins by measurement of the stable metabolite 6-keto-prostaglandin $F_{1\alpha}$. The results are shown in the *Table*.

	Prostacyclin release (pg cm^{-2})	
	Basal	Stimulated
Control	115(29)	248(49)
Dilated	71(20)	128(35)
Dilated and seeded	366(86)	256(62)

Values are mean(s.e.m.)

Data were initially analysed using a one-way ANOVA ($P < 0·01$, Kruskal–Wallis test), and specific differences were compared using the Wilcoxon paired rank test. Significant differences were found for stimulated prostacyclin release between control vein and dilated vein, and between dilated and seeded veins ($P < 0·05$).

These results show that endothelial seeded angioplasty sites produce a high prostacyclin concentration *in vitro*, which may have important applications *in vivo*.

Oxidants, antioxidants and venous ulceration

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In patients with venous hypertension neutrophils are trapped within the dependent limb and, on re-elevation, reperfusion of ischaemic tissue may promote the release of free radicals. Glutathione peroxidase, a naturally occurring antioxidant, protects against free radical damage. Free radical production was investigated in patients with venous ulceration after the ischaemia of dependency and reperfusion of re-elevation, and related to antioxidant levels in these patients.

Blood was sampled from a calf varix in ten patients with venous ulceration after lying for 30 min, dependency for 30 min and a further 30 min of re-elevation, and at the same intervals in six patients who lay supine for 90 min. Neutrophil superoxide release was measured using a colorimetric cytochrome *c* assay (nanomoles per 10^6 neutrophils per 20 minutes). Glutathione peroxidase was measured in ten patients with venous hypertension and ten controls using an indirect spectrophotometric method which measures the rate of conversion of NADPH to NADP (Δabsorbance per minute per millilitre of plasma).

In patients with venous disease, mean(s.e.m.) plasma glutathione peroxidase was lower than in controls (2·91(0·24) *versus* 3·37(0·32); $P < 0·05$, Wilcoxon test). Neutrophil superoxide release rose from 15·9(2·1) to 26·9(3·8) on dependency and remained elevated at 24·6(5·1) after 30 min of re-elevation ($P < 0·05$, Wilcoxon test). Neutrophil superoxide release did not vary over time in controls at 14·1(2·6) initially and 14·5(2·9) after 90 min.

In patients with venous ulceration, glutathione peroxidase was reduced and free radicals were generated on dependency and re-elevation; this is a response characteristic of the ischaemic-reperfusion injury. Unopposed free radical production may be important in the pathogenesis of venous ulceration.

Vascular endothelium in Raynaud's phenomenon

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Vascular endothelium controls blood vessel calibre by producing prostacyclin (PGI_2) and endothelium-derived relaxing and contracting factors (EDRF and EDCF) Endothelial EDRF synthesis was studied in eight patients with Raynaud's phenomenon and eight matched controls at 21 ± 1°C PGI_2 synthesis was abolished by aspirin ingestion before the study A sequential series of infusions alternating with saline as control was administered at a rate of 1 ml min^{-1} via the radial artery. The infusions contained acetylcholine chloride (ACh) 110 nmol ml^{-1}, ACh 550 nmol ml^{-1}, L-arginine 50 μmol ml^{-1}, PGI_2 2·5 ng ml^{-1} or glyceryl trinitrate 4·5 nmol ml^{-1} Digital artery diameter and cutaneous temperature were monitored. Mean brachial artery pressure and digital cutaneous flow were comparable in the two groups at the start of the study

Infusions	Patients	P*	Controls	P*
Digital artery diameter change from baseline in response to infusions (mm)				
ACh				
110 nmol ml^{-1}	+0·05(0·04)	n.s.	+0·09(0·04)	<0·03
550 nmol ml^{-1}	+0·05(0·05)	n.s	+0·13(0·08)	<0·04
L-Arginine	+0·03(0·07)	n.s	+0·05(0·07)	n.s
PGI_2	+0·12(0·06)	<0·03	+0·05(0·07)	n.s
Glyceryl trinitrate	+0·16(0·07)	<0·03	+0·09(0·05)	<0·03
Temperature change from baseline in response to infusions (°C)				
ACh				
110 nmol ml^{-1}	+0·40(1·07)	n.s.	+3·64(1·88)	<0·02
550 nmol ml^{-1}	+1·00(1·55)	n.s	+4·20(2·79)	<0·02
L-Arginine	+0·78(2·47)	n.s.	+0·58(1·39)	n.s
PGI_2	+3·05(2·25)	<0·02	+2·90(2·19)	<0·02
Glyceryl trinitrate	+3·29(1·75)	<0·02	+2·51(2·76)	n.s.

*Wilcoxon paired rank test; n.s., not significant

The difference in the response of the digital vasculature in the two groups to ACh infusion, with significant vasodilatation occurring only in controls, was statistically significant ($P < 0{\cdot}05$, Mann–Whitney *U* test). Although vasodilatation to PGI_2 and glyceryl trinitrate occurred in both groups, a significantly greater increase in digital arterial diameter occurred in patients with Raynaud's phenomenon ($P < 0{\cdot}02$, Mann–Whitney *U* test). The results obtained in this study support the hypothesis that a dysfunction of the vascular endothelium resulting in diminished EDRF synthesis may contribute to the development of vasospasm in Raynaud's phenomenon.

Human pancreatic islet purification after storage of the pancreatic digest in University of Wisconsin solution

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The ability to purify human pancreatic islets before transplantation relies on the separation of the less dense islets from the collagenase-digested pancreatic tissue using large scale discontinuous density gradients The pancreatic digest is stored for up to 1 h during this process, and such storage in minimal essential medium (MEM) causes a deterioration in the subsequent tissue separation. To investigate whether storage of the digest in University of Wisconsin solution (UW) could prevent this, part of the human pancreatic digest from seven subjects was stored in either MEM or UW for a period of 1 h After density gradient centrifugation, the density and consequent separation of the islet and exocrine tissue were analysed using insulin and amylase assays.

Storage in MEM was found to decrease the density of the exocrine tissue more than that of the islets, causing exocrine contamination of the purified islets to increase Storage in UW for 1 h, on the other hand, increased the density of the exocrine tissue, and compared with storage in MEM resulted in a significant decrease in exocrine contamination ($P = 0{\cdot}036$, Wilcoxon matched pairs signed rank test). Storage in UW not only prevented the deterioration but in five of the seven samples improved purification Although statistically this was not significant, in practice this improvement was so dramatic that digest could be purified from some samples where no islets could be separated initially

In conclusion, the storage of pancreatic digest in UW for 1 h before islet separation increases the density of pancreatic exocrine tissue, improving the purification of human islets before transplantation.

Regulation of digital blood flow by female sex hormones

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Fluctuations in levels of female sex hormones may be responsible for the high prevalence of Raynaud's disease among premenopausal women. The aim of the study was to establish a hormonal basis for cold sensitivity In all, 42 premenopausal women (22 with Raynaud's disease and 20 controls) underwent a cold stress test throughout one menstrual cycle Experiments were performed during peaks and troughs of circulating oestradiol and progesterone. Subjects were exposed to total body cooling and total body warming in an environmental chamber. Body core temperature was monitored to assess central thermoreceptor activation. Digital blood flow was measured using strain gauge plethysmography and skin thermometry. The results are shown in the *Table*.

	Blood flow at rest (ml per 100 ml per min)		Blood flow after cold stress test (ml per 100 ml per min)	
Day of cycle	Control	Raynaud's disease	Control	Raynaud's disease
1–5	39 (27–53)	17 (4–24)†	33 (18–50)	10 (2–20)†
12–13	42 (19–52)	22 (2–34)*	15 (7–25)‡	3 (1–9)†§
21–23	35 (19–40)	14 (5–33)*	23 (4–37)§	3 (1–8)†§

Values are median (interquartile range) *$P < 0{\cdot}01$; †$P < 0{\cdot}005$ (Mann–Whitney *U* test), ‡$P < 0{\cdot}01$, §$P < 0{\cdot}001$ (Wilcoxon test)

The results demonstrate that subjects with Raynaud's disease are significantly less cold-tolerant than controls when the effects of female sex hormones are controlled. Moreover, recovery from a cold stress test is fastest, in both groups, during menstruation It is concluded that the stage of the menstrual cycle should be controlled, where possible, in the assessment of cold sensitivity and that female sex hormones play a significant role in regulating digital blood flow This effect appears to be mediated through their central action on the thermoregulatory centre and by a peripheral mechanism that alters digital vessel reactivity

Persistent and dose-dependent reduction of rabbit intimal hyperplasia with α-adrenergic blockade

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Preliminary studies have shown that α_1-adrenergic blockade may reduce the development of intimal hyperplasia in the rabbit aorta. In this study a newer, more specific α_1-antagonist has been used to examine whether this effect is dose dependent and related to the duration of administration

Forty-eight New Zealand White rabbits underwent endothelial denudation of the abdominal aorta using a Fogarty embolectomy balloon catheter. Control rabbits were killed either 1 or 12 weeks later Test rabbits were given low- (2 mg) or high-dose (8 mg) doxazosin daily and killed at either 1 or 12 weeks. The aortas were harvested after fixation *in situ* with 4 per cent glutaraldehyde, and neointimal hyperplasia was measured using an *x*–*y* digitizer The results are expressed as a percentage of luminal reduction

	Control ($n = 8$)	2 mg Doxazosin ($n = 8$)	8 mg Doxazosin ($n = 8$)
1 week	14·8 (6·6–40·0)	7·7 (2·7–10·1)*	8·2 (0·9–11·5)*
12 weeks	32·6 (18·1–44·8)	25·7 (5·5–50·3)‡	5·5 (2·7–16·2)†

Values are median (range). *$P < 0{\cdot}01$, †$P < 0{\cdot}0001$; ‡P not significant *versus* respective controls (Mann–Whitney *U* test)

It is concluded that α_1-adrenergic blockade significantly reduces neointimal hyperplasia, and that this effect is dose dependent and related to the duration of administration of the drug

Effects of Gram-negative endotoxaemia during orthotopic liver transplantation

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Gram-negative endotoxaemia has been documented during orthotopic liver transplantation (OLT), but it is unclear whether it is harmful[1]. Endotoxaemia can initiate shock and hepatorenal syndrome, and activates macrophages, antigen-processing cells, and T and B lymphocytes[2], via cytokines released from mononuclear phagocytes on binding endotoxin. The present study investigated whether endotoxaemia is associated with release of cytokines in OLT recipients.

Twelve consecutive recipients (six men and six women, aged 19–63 (median 48·5) years) were investigated. Indications for OLT were primary biliary cirrhosis ($n = 5$), acute hepatic failure ($n = 2$), primary sclerosing cholangitis ($n = 1$), cholangiocarcinoma ($n = 1$), alcoholic cirrhosis ($n = 2$) and cryptogenic cirrhosis ($n = 1$) Blood samples were collected before operation, during OLT (anhepatic and reperfusion phases), and 12 and 72 h after operation, into endotoxin-free heparinized tubes. Endotoxaemia was quantitated by a chromogenic substrate/*Limulus* amoebocyte lysate bioassay. Plasma tumour necrosis factor (TNF), interleukin 1 (IL-1) and serum interleukin 6 (IL-6) were determined by enzyme-linked immunosorbent assay (sensitivity 10 ng l^{-1}).

Plasma endotoxin levels rose significantly from preoperative values (median 79·8 ng l^{-1}) during the anhepatic phase (median 96·0 ng l^{-1}; $P < 0{\cdot}05$, Wilcoxon test), declining significantly 12 and 72 h after operation (median 72·0 and 47·0 ng l^{-1} respectively, both $P < 0{\cdot}001$). Six subjects developed marked perioperative endotoxaemia (> 100 ng l^{-1}). Although detectable TNF was discovered in five of the 12 recipients (20–100 ng l^{-1}), IL-1 in one (13 ng l^{-1}) and IL-6 in four (80–1000 ng l^{-1}), endotoxaemia and plasma TNF, IL-1 or serum IL-6 were not significantly correlated, nor did any parameter predict graft function, rejection episodes or outcome. The results of the present study suggest that, although endotoxaemia occurs frequently during OLT, this does not necessarily provoke cytokine responses, and thus may not be harmful.

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2 Morrison DC, Ryan JL. Bacterial endotoxins and host immune responses. *Adv Immunol* 1988; **28**: 293–413

Influence of nifedipine, the dopamine agonist fenoldopam, enalapril and a thromboxane receptor antagonist (L607596) on a rat model of cyclosporin nephrotoxicity

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Using a new model employing repeatable single-injection isotopic techniques for measuring glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), this study investigated the influence of a variety of vasoactive agents on a rat model of low-dose cyclosporin nephrotoxicity

Groups of ten Sprague–Dawley rats (280–320 g) received intraperitoneal cyclosporin 5 or 7·5 mg kg^{-1} day^{-1} or cremaphor vehicle, with either nifedipine 0·5 mg kg^{-1} day^{-1}, fenoldopam 10 mg kg^{-1} day^{-1}, enalapril 5 mg kg^{-1} day^{-1}, L607596 20 mg kg^{-1} day^{-1} or their vehicles. GFR and ERPF were measured before and after 14 days of treatment

Cyclosporin caused a marked reduction in GFR (−41 per cent, $P < 0{\cdot}0001$, Student's paired *t* test), ERPF (−58 per cent, $P < 0{\cdot}0001$) and filtration fraction (FF) (−14 per cent, $P < 0{\cdot}001$).

Enalapril and fenoldopam prevented the reduction in ERPF seen with cyclosporin, but both failed to restore GFR or FF. Nifedipine also reversed the fall in ERPF (+14 per cent, $P < 0{\cdot}05$) and prevented a fall in GFR, but FF (−5 per cent, $P < 0{\cdot}0001$) remained depressed. Thromboxane receptor blockade completely restored GFR and FF to normal, but ERPF (−10 per cent, $P < 0{\cdot}05$) remained significantly reduced.

Cyclosporin nephrotoxicity is characterized by two mechanisms that reduce GFR. It causes renal arteriolar vasoconstriction but has a second mechanism independent of this, possibly glomerular mesangial cell contraction. Renal vasodilators have a beneficial effect in restoring plasma flow, but do not reverse the glomerular changes induced by cyclosporin. Thromboxane A_2 seems to be an important mediator of this glomerular mechanism.

Effect of nifedipine on immediate graft function in cyclosporin-treated renal transplant patients: a prospective randomized study

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It has been proposed that calcium channel blockers may reduce the frequency of delayed graft function in cadaveric renal transplantation by minimizing ischaemic cell injury. To investigate the effects of oral nifedipine, 68 adult renal transplant recipients were randomized before operation to one of three regimens: 1 (high-dose cyclosporin A, initial dose 17 mg kg^{-1} day^{-1}); 2 (regimen 1 plus nifedipine), 3 (low-dose cyclosporin A, initial dose 10 mg kg^{-1} day^{-1}, plus azathioprine 1 mg kg^{-1} day^{-1}). All three groups received identical steroid regimens. Blockers of all types were avoided in groups 1 and 3.

Treatment regimen	Frequency of immediate graft function (no. of patients)
1: High-dose cyclosporin A	12 of 21 (57)
2: High-dose cyclosporin plus nifedipine	22 of 24 (92)
3: Triple therapy	16 of 23 (70)

Values in parentheses are percentages

Immediate graft function (dialysis independence by day 4) was seen most frequently in group 2 ($P < 0{\cdot}02$). The three groups did not differ in donor or recipient age, human leucocyte antigen matching, ischaemic or anastomosis times, frequency of early rejection or whole blood cyclosporin A levels. These data indicate that calcium channel blockade with oral nifedipine significantly improves immediate graft function

Method of reducing graft *versus* host reactivity in small bowel transplantation

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There is extensive migration of graft cells to host lymphoid tissues after small bowel transplantation with cyclosporin A immunosuppression. These cells have the potential to cause graft *versus* host disease This study examines the effect of delaying the start of cyclosporin A treatment on subsequent graft cell migration. Transplantation was carried out in rats from PVG donors to DA recipients in four groups: 1 (no immunosuppression, $n = 5$); 2 (cyclosporin A, 15 mg kg^{-1} day^{-1}, from day 0, $n = 6$); 3 (cyclosporin A from day 3 after transplantation, $n = 6$); and 4 (cyclosporin A from day 3, $n = 5$). On day 7, tissues from the first three groups were harvested and stained with strain-specific monoclonal antibodies (OX27 *versus* PVG, MN4 *versus* DA) using an immunohistochemical technique. In group 4, graft tissues were harvested on days 14–20.

	Median graft cell infiltration of host tissues 7 days after transplantation (%)		
Tissue	No treatment	Cyclosporin A	Delayed cyclosporin A
Spleen	0	47 (46–49)	1 (0–4)
Mesenteric node	3 (1–4)	47 (46–51)	1 (0–3)
Peyer's patch	25 (19–32)	41 (33–48)	1 (0–5)

Values in parentheses are ranges. $P < 0{\cdot}01$ for differences between treatment groups (Wilcoxon test)

Histological signs of acute rejection were present in the untreated group (1) but not in groups 2 (full course of cyclosporin A) or 4 (delayed start cyclosporin A studied after day 14). In group 3 (delayed start cyclosporin studied at day 7), there was evidence of mild rejection only

Delayed cyclosporin treatment reduces the survival of graft leucocytes within host lymphoid tissues without permitting severe irreversible rejection Such strategies may be of value in obviating graft *versus* host disease after small bowel transplantation.

Risk of neoplasia in the renal transplant population

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Patients on long-term immunosuppressive therapy have an increased incidence of cancer[1] The records of 778 renal allograft recipients undergoing transplantation over a 20-year period were examined The search revealed 62 patients (8 per cent) with cancer, a higher incidence than expected in a European transplant population Thirty-three patients were diagnosed as having skin cancer (17 with squamous cell carinoma, seven with Bowen's disease and nine with basal cell carcinoma), but no patients developed malignant melanoma or Kaposi's sarcoma Non-cutaneous tumours consisted of 11 urogenital, five gastrointestinal, seven lymphoreticular, three lung or bronchus, three larynx and six others. Six patients had more than one tumour type

As expected, the incidence of malignancy increases with age at transplantation under 20 years, two of 92 (2 per cent), 20–59 years, 54 of 648 (8 per cent), over 60 years, six of 38 (16 per cent). The incidence of malignancy appears not to be related to the type of immunosuppressive therapy (16 of 62 cyclosporin, 46 of 62 azathioprine), although the follow-up for patients receiving cyclosporin is shorter The median (interquartile range) interval from transplantation to diagnosis of malignant disease was 65 (32–113) months, although the interval for skin cancers was significantly longer at 93 (59–133) months when compared with the remainder at 46 (14–82) months ($P < 0.002$, Mann–Whitney *U* test)

The risk of malignancy increases with time after transplantation The risk of developing a neoplastic lesion in the first 10 years after transplantation is 11 per cent, but by 15 years this risk has risen to 26 per cent.

The full extent of the problem of neoplasia in the European renal transplant population is only now becoming apparent as patients and grafts survive longer, reaffirming the need for life-long surveillance of these patients.

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Selective screening for cardiac risk

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Perioperative myocardial infarction (MI) is the predominant cause of death after aortic surgery. Some authors advise that all patients undergo sophisticated tests of cardiac function, radioisotope scans or multiple uptake gated scans, but this is impractical and possibly unnecessary The alternative is to screen selectively, with clinical examination as the first step.

The clinical data recorded from 555 consecutive patients were analysed to identify risk factors predisposing to MI. Of 35 patients who had a perioperative MI, 12 died. There were eight deaths in 460 patients thought to be at low risk and four deaths in 95 patients assessed as at high risk Multiple logistic regression analysis identified four factors independently predictive of MI Relative risk ratios were transient ischaemic attacks 5·08, raised serum creatinine 3·66, age above 60 years 3·00, and history of MI or angina 2·74. A scoring system based on weighted values of these ratios identified 153 patients as high risk, including all those who had a perioperative MI

A weighted clinical risk score is a practical first step in identifying patients at risk of MI, and would reduce the number of patients for whom sophisticated tests of cardiac function are necessary

Aetiology of periductal mastitis (duct ectasia)

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The clinical syndrome of recurrent non-lactational breast abscesses (BA) and mammillary fistula associated with periductal mastitis (DE) leads to considerable morbidity in young women. The aetiology of DE remains unknown[1]. Cigarette smoking is known to exert anti-oestrogenic effects[2].

The aim of this study was to determine the risk factors associated with the development of DE by comparing the reproductive history and smoking habits of all patients with either non-lactational BA or biopsy-proven DE with those of female age- and sex-matched hospital controls. In all, 85 women with BA (mean age 35·8 (range 11–69) years), 93 women with DE (mean age 39·7 (range 17–80) years) and 128 hospital controls (mean age 35·7 (range 15–73) years) were compared. Univariate analysis showed no difference between groups for menarche, parity and age at first live birth Among controls, 56 of 128 women (44 per cent) had ever smoked cigarettes, compared with 57 of 85 women (67 per cent) with BA and 69 of 93 women (74 per cent) with DE ($P < 0.001$, relative risk 3·9, 95 per cent confidence interval 3·74–4·06). Women with DE were less likely to be current pill users ($P < 0.05$, relative risk 1·93, 95 per cent confidence interval 1·6–2·24). Women with BA who smoked were more likely to have anaerobic breast abscesses ($\chi^2 = 4.2$, $P < 0.05$) and recurrence of abscess ($\chi^2 = 7.3$, $P < 0.01$). Cigarette smoking is associated with the development of DE and exacerbates the disease. Stopping smoking may be a useful therapeutic manoeuvre in patients with DE

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Small bowel absorption depends on luminal oxygen and energy substrate content

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Absorption of luminal contents is reduced in small bowel obstruction The influence of luminal oxygen and small bowel energy substrate solutions on absorption in obstructed small intestine was studied.

Isolated 5-cm sections of small bowel (with intact blood supply) in four groups of ten male rats were injected with 0·4 ml energy substrate solution (glucose 10 mmol l^{-1}, glutamine 5 mmol l^{-1}) or ketone bodies (acetoacetate and hydroxybutyrate) 10 mmol l^{-1} or control saline (0·9 per cent) solution. Solutions were either aerated or nitrogenated to remove dissolved oxygen After 1 h, the sections of bowel were excised and luminal contents determined to calculate the volume absorbed or secreted

	Contents secreted (+) or absorbed (–) (mg)			
	No fluid added	Nitrogenated	Aerated	*P**
Glucose	+30 (0 to 270)	–80 (–260 to +10)	–250 (–260 to +10)	<0·02
Glutamine	+70 (10 to 370)	–180 (–300 to –110)	–210 (–250 to –90)	n s
Ketone bodies	+70 (10 to 370)	–188 (–320 to –70)	–276 (–370 to –140)	<0·05
Saline control	+60 (0 to 320)	–125 (–220 to +90)	–215 (–280 to –190)	<0·05

Values are mean (range) *Nitrogenated *versus* aerated (Mann–Whitney *U* test), n s, not significant

Absorption of luminal contents is reduced in small bowel obstruction, but this can be reversed by administration of luminal energy substrates and oxygen. Absorption in small bowel obstruction depends on energy substrates and oxygen present in the lumen, which it does not obtain in sufficient quantity from its blood supply.

Effect of splenectomy on early host response to intra-abdominal infection

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Septic sequelae after splenectomy are well recognized, but their mechanisms are unclear. Macrophage activation may be detrimental during the acute septic response. The present study evaluated the effect of splenectomy on peritoneal macrophage activation.

In study 1 (*in vitro*), female mice were randomized to receive no treatment, laparotomy or laparotomy and splenectomy. Twenty-four hours later, peritoneal cells were harvested and studied for cell kinetics and macrophage superoxide anion (O_2^-) production.

In study 2 (*in vivo*) mice were randomized to laparotomy or laparotomy plus splenectomy groups, subjected to simultaneous caecal ligation and puncture, and observed for survival at 24 h.

	Study 1 ($n = 40$)			Study 2 ($n = 50$)
	Total cells (%)	Macrophage (%)	O_2^- (nmol)	Survival (%)
Control	5(0·3)	47(2)	0 5(0)	—
Laparotomy	9(0 7)	42(2)	1 7(0·2)	56
Laparotomy plus splenectomy	18(3)*	25(3)†	2 5(0 7)*	32‡

Values are mean(s e m). *$P < 0$ 05, †$P < 0$ 001; ‡$P < 0$ 02 *versus* other groups

Laparotomy was associated with an influx of inflammatory cells into the peritoneal cavity, but percentage macrophage content was unaltered. Laparotomy and splenectomy was associated with a significant increase in inflammatory cells in the peritoneal cavity, but percentage macrophage content was significantly reduced. Superoxide anion release was increased after injury, but significantly so only in the laparotomy plus splenectomy group ($P < 0$ 05). Highest levels of macrophage activation (laparotomy plus splenectomy) correlated with the significantly higher mortality rate seen in this group. These findings demonstrate a novel role for the spleen in regulating peritoneal cell fluxes and function during the acute inflammatory response, and indicate a mechanism through which splenectomy may predispose to mortality from early sepsis.

Impairment of macrophage activation and granuloma formation by protein malnutrition

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Protein malnutrition predisposes to infection by intracellular pathogens, but the basis for this predisposition is unclear The capacity of macrophages to respond to activation stimuli and to form granulomas with T cells is critical for host defence against intracellular pathogens. The influence of acute protein malnutrition on these parameters was assessed in 6-week-old Swiss mice ($n = 240$) randomized to receive a 24 per cent regular diet or an isocaloric 2·5 per cent low protein diet for 3 weeks. Feeding a 2 5 per cent diet for this time resulted in a 10 per cent loss in body-weight and a mean(s.e.m.) serum albumin level of 2·2(0 01) g l^{-1} compared with an albumin level of 3·6(0 5) g l^{-1} in mice fed a regular diet.

Peritoneal macrophage activation was assessed by the production of superoxide anion in response to endotoxin (lipopolysaccharide (LPS), 0·5 μg), γ-interferon (IFN-γ, 100 units ml^{-1}) and intravenous BCG (5×10^7 live organisms) infection. Superoxide generation was measured as the reduction of ferricytochrome *c* by activated macrophages stimulated with phorbol myristate acetate. Granuloma formation (mean of four experiments) was quantified in the liver, lung and spleen of BCG-infected mice after 21 days.

	Superoxide production (nmol per mg protein per 90 min)			Granuloma (arbitrary units)		
Diet	LPS	γ-Interferon	BCG	Liver	Lung	Spleen
24 per cent	389(10)	484(55)	782(27)	2 3	3 0	4 0
2 5 per cent	223(47)*	253(56)*	-673(41)*	1 0*	1 3*	1 0*

*$P < 0$ 05 (Student's *t* test)

Protein malnutrition significantly impaired macrophage activation and granuloma formation. These data suggest mechanisms that may underlie the impaired capacity of the protein-malnourished patient to reject intracellular pathogens.

Obstructed micturition in constipated women

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Of numerous hypotheses advanced to explain retention of urine in women, proctological causes have seldom attracted attention, although rectocele is commonly observed in women with voiding dysfunction. We have developed a new investigation allowing the synchronous radiographic visualization of the bladder and rectum, intrarectal and intravesical pressure monitoring, and electromyographic surveillance of puborectalis muscle activity during defaecation and micturition These combined studies have unexpectedly revealed that many of these women show inappropriate contraction of the puborectalis during micturition.

Sixteen female patients with chronic constipation (mean age 45 (range 21–83) years) suffering with urological symptoms have been investigated by simultaneous dynamic integrated electromyographic proctography and cystometrography. Six were able to micturate normally. Ten micturated by abdominal strain, and of these all but two had an inappropriate contraction of the puborectalis during micturition (mean electromyographic recruitment 236 (range 50–500) per cent), compared with only one in the group who micturated normally ($P = 0{\cdot}02$, Fisher's exact test). Of ten in the abnormal micturation group, eight had a rectocele, compared with four of six in the normal group ($P = 0$ 5, Fisher's exact test) However, in the abnormal micturition group, seven of eight women with a rectocele also had inappropriate contraction of the puborectalis, compared with none of four women who were able to micturate normally ($P = 0{\cdot}02$, Fisher's exact test). These results suggest that, in women with obstructive voiding in whom there is no obvious urological abnormality, a proctological or pelvic floor abnormality should always be considered, and a combined study may help to elucidate the underlying condition

Mechanical ventilation and postoperative morbidity after major surgery

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Overnight mechanical ventilation has become accepted practice if respiratory problems after major surgery are anticipated, but weaning difficulties are frequently encountered Evidence is emerging that ventilatory support may be associated with considerable alveolar trauma. This prompted a policy change in January 1990, making early extubation mandatory in all but the most seriously compromised patients undergoing elective oesophagectomy. Two patient groups were compared; group 1 ($n = 36$) underwent oesophagectomy in the year before the change in policy, and group 2 ($n = 45$) in the year after the change. Both groups were comparable for age, sex ratio and respiratory risk factors.

	Group 1 ($n = 36$)	Group 2 ($n = 45$)	P*
Ventilated overnight	28 (78)	7 (16)	<0 001
Prolonged ventilation	10 (28)	2 (4)	<0 005
Reventilated	7 (19)	0 (0)	<0 002
Mean time on ventilator (days)	4·6	1·1	<0 05
90-Day mortality rate	6 (17)	2 (4)	<0 05
Mean intensive care unit stay (days)	9·8	5 9	<0·05
Mean postop. stay (days)	22·1	17·8	<0 01

Values in parentheses are percentages. *χ^2 test and Mann–Whitney *U* test; n.s , not significant

Early extubation was possible in 84 per cent of patients with no adverse sequelae, but with a significant reduction in morbidity rate No patient required ventilation as a delayed measure, and the total ventilator time was significantly reduced. These findings are consistent with experimental and clinical evidence linking ventilatory alveolar trauma to respiratory complications, and support the view that prompt extubation avoids this added postoperative risk

Perioperative low-dose recombinant interleukin 2 and immune function in patients undergoing surgery for colorectal cancer

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Surgical resection for gastrointestinal cancer impairs cellular immunity, which may facilitate malignant dissemination. The aim of the present study was to determine whether perioperative administration of low-dose subcutaneous recombinant interleukin 2 (rIL-2) can ameliorate this suppression.

Twenty patients undergoing surgical resection for colorectal cancer were randomized to a control group or to receive rIL-2, $1{\cdot}8 \times 10^6$ units m^{-2} twice a day, from the day before operation for 5 days. This regimen produced no clinical effects other than low grade pyrexia. Immunological studies of both lymphocyte function (assessed by chromium-51 release assay) and subset number (designated by cluster of differentiation (CD) number and analysed by flow cytometry) were performed before operation and on days 1, 4, 7 and 10 after operation.

Natural killer (NK) cell and lymphokine-activated killer (LAK) cell cytotoxicity (to tumour cell line targets K562 and DAUDI, respectively) fell after operation in the control group ($P < 0{\cdot}01$ and $P < 0{\cdot}05$), mirrored by a fall in NK (CD16) and LAK (CD56) cell number ($P < 0{\cdot}05$). In all patients receiving rIL-2, these effects were reversed.

Total T cell (CD3) expressed was lower on days 1 and 4 in both the control and treatment groups ($P < 0{\cdot}05$ and $P < 0{\cdot}01$), but only those receiving rIL-2 had a subsequent (days 7 and 10) rebound T cell lymphocytosis ($P < 0{\cdot}01$). On day 1, there was a fall in the helper/inducer (CD4) to cytotoxic/suppressor (CD8) ratio in the rIL-2 group ($P < 0{\cdot}02$), which did not occur at any other time and was not observed in the control group. The rIL-2 group demonstrated marked immunoactivation with up-regulation of both soluble rIL-2 receptor (CD25) and memory T cell (CD45 RO) expression ($P < 0{\cdot}005$ and $P < 0{\cdot}02$) on days 7 and 10.

In conclusion, perioperative low-dose rIL-2 prevents the immunosuppression associated with surgery for colorectal cancer.

Interstitial photodynamic therapy for patients with colorectal hepatic metastases

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Focal destruction of colorectal hepatic metastases may have a place in the management of patients unsuitable for hepatic resection. We have designed a new approach whereby a light-sensitive non-toxic drug, haematoporphyrin derivative (HpD), is activated by light locally within the metastases to achieve tumour necrosis.

Thirteen patients (five men, eight women) with 21 metastases (four solitary) were sensitized with intravenous HpD (111 mg m^{-2}). A custom-designed light delivery system was used; its four 200-μm optical fibres were geometrically positioned within the metastases 48 h after sensitization with HpD. Laser light (630 nm) from a copper vapour laser was applied to deliver 50 J to each fibre. This treatment was performed percutaneously in seven patients and during laparotomy in six others. Metastases were imaged before and after treatment using computed tomography, and their volumes measured by planimetry.

Because the metastases treated varied in size, the response to treatment was quantified using the mean metastasis relative volume growth at 12–14 weeks, and treated (18) and non-treated (three) metastases (control) were compared by Mann–Whitney *U* test.

	Volume of metastasis (mm^3)		Metastasis relative volume growth (mm^3)
	Before treatment	At 12–14 weeks	
Treated	27·60(15·67)	25·99(14·64)	0·94(0·28)*
Non-treated	24·27(8·75)	53·47(16·88)	2·13(0·15)*

Values are mean(s.d.). $^*P < 0{\cdot}01$ (Mann–Whitney *U* test)

Interstitial photodynamic therapy is a minimally invasive technique which can be applied either percutaneously or at laparotomy. These data show that interstitial photodynamic therapy significantly reduces growth rates of metastases, compared with untreated controls.

Changes in stage of colorectal cancers at presentation

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It has been suggested that, by the time patients with colorectal cancer have symptoms, reducing the delay to diagnosis does not improve the stage of the disease. To identify whether the stage of disease at presentation is changing, this study investigated the stage distribution of cancers among the control group subjects from a randomized controlled trial of faecal occult blood screening for colorectal neoplasia.

Since 1981, 77645 subjects have been randomized to the control group (identified but not offered screening). Of these, 405 cancers have presented symptomatically. 206 from 1981 to the end of 1988 and 199 from 1989 to 1991. The stage of presentation has been determined for all subjects in the two time periods.

	Cancers diagnosed in the control group	
Dukes' classification	1981–1988	1989–1991
Early A	21 (10·4)	35 (18·5)
B	58 (28·7)	75 (40·2)
Late C	67 (33·2)	49 (25·6)
'D'	56 (27·7)	34 (16·3)

Values in parentheses are percentages. $\chi^2 = 12{\cdot}65$, 1 d.f., $P < 0{\cdot}001$ (early *versus* late groups)

Significantly more early-stage cancers have presented since 1989 than previously, although there has been no change in the number of cancer polypectomies (five before 1989, four since). However, more rectal cancers are now being diagnosed early ($P < 0{\cdot}001$), although the stage of presentation of colonic carcinoma has not significantly changed.

These data suggest that the differences may be due to an increased awareness of symptoms by both patients and doctors, rather than to the greater availability of accurate diagnostic facilities.

Aprotinin as an anticoagulant

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The serine protease inhibitor aprotinin significantly reduces transfusion requirements during surgery. Whether this benefit is associated with an increased tendency to thrombosis has not been studied. The effect of aprotinin in an experimental arterial thrombosis model was investigated. In 17 male Sprague–Dawley rats, the infrarenal aortas were replaced with 1·0 mm diameter polytetrafluoroethylene grafts of varying lengths. The mean(s.d.) times to graft occlusion, recorded by palpation, Doppler ultrasonography and a distal bleeding test, were 20·2(1·8), 35·8(6·1) and 43·7(6·6) min for grafts of 10, 7·5 and 5·0 mm respectively ($r = -0{\cdot}98$, $P < 0{\cdot}05$).

Using this model the effects of saline, aprotinin (4 mg kg^{-1} intravenous loading dose and 1 mg kg^{-1} h^{-1} infusion) and heparin (100 units kg^{-1} intravenous loading dose and 15 units kg^{-1} h^{-1} infusion) on thrombosis were investigated, singly and in combination (graft length 10 mm).

Group ($n = 6$)	Time to graft thrombosis (min)	Activated partial thromboplastin time (s)	Prothrombin time (s)	Bleeding time (min)
Saline	20·2(1·8)	17·2(3·3)	21·9(3·0)	2·9(0·7)
Aprotinin	71·7(20·4)	40·0(15·5)*	29·4(6·2)*	3·0(0·9)
Heparin	118·3(26·4)*†	>300*	40·7(2·5)	22·5(2·3)*
Heparin plus aprotinin	109·5(15·2)*	>300*	39·9(14·5)*	18·9(4·1)*

$^*P < 0{\cdot}05$ *versus* control, $^†P < 0{\cdot}05$ *versus* aprotinin

These data show that high doses of aprotinin do not increase thrombosis, but induce significant anticoagulation, which is not associated with abnormalities in bleeding time. The simultaneous administration of heparin and aprotinin does not have a cumulative anticoagulant effect. We speculate that aprotinin may be the ideal anticoagulant in surgery.

Exogenous growth hormone attenuates abnormal water distribution in critically ill surgical patients

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Catabolic illness is associated with fluid retention and expansion of the extracellular space. To determine the effect of recombinant human growth hormone (GH), a potent anabolic agent, on body fluid compartments during life-threatening illness, 17 stable catabolic patients with surgical complications, major burns or multiple injuries and at least one organ failure were randomized either to continue standard intensive care support (control group) or additionally receive GH 10 mg day^{-1} (GH group). Parenteral and/or enteral nutrition was provided to meet energy (mean 34 kcal kg^{-1} day^{-1}) and protein (mean 1·3 g kg^{-1} day^{-1}) requirements. Total body water (TBW), extracellular water (ECW) and intracellular water (ICW) were determined by the deuterium oxide (10 g) and sodium bromide (3 per cent, 50 g) dilution technique at the outset and after 2 weeks of study. Body-weight (BW) and relevant clinical and nutritional data were obtained daily. There were no statistically significant differences between groups in terms of weight, height, age, sex, nutritional intake or hospital day of study entry The mean(s.e.m.) changes in weight and body water compartments over 2 weeks, as well as the ECW:TBW ratios at the beginning ($t = 0$) and end ($t = 2$) of the period are shown in the *Table*

	Control ($n = 7$)	Growth hormone ($n = 10$)
Change in		
BW (kg)	−3·4(2·7)	−1·8(2·6)
TBW (litre)	−0·5(1·0)	−0·9(1·7)
ECW (litre)	+5·2(1·8)	−1·2(1·4)*
ICW (litre)	−5·8(1·5)	+0·2(0·6)*
ECW.TBW		
$t = 0$	0·46	0·57†
$t = 2$	0·49	0·47

Values are mean(s.e.m.). *$P < 0·001$ *versus* controls (Mann–Whitney *U* test); †$P = 0·001$ *versus* $t = 0$ (ANOVA)

BW and TBW decreased in most patients and could not be used to differentiate between groups. A marked expansion in ECW occurred in the control patients, which was associated with a loss of ICW and disturbance of ECW:TBW ratio. In contrast, patients receiving GH maintained ECW and ICW levels and normal fluid distribution Because preservation of body cell mass is closely related to maintenance of ICW, these findings suggest that GH can prevent the loss of a critical component of lean tissue in catabolic patients. We conclude that GH administration attenuates abnormal fluid distribution during critical illness and, as GH is known to improve nitrogen balance, that it can be used to stabilize body cell mass in catabolic surgical patients.

Inhibitory transmission in the human internal anal sphincter: the role of nitric oxide

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Internal anal sphincter (IAS) relaxation is mediated by non-adrenergic non-cholinergic (NANC) intramural nerves, but the nature of the neurotransmitter(s) involved is unknown This study explored the role of nitric oxide in this process.

Small strips of IAS circular muscle (18 strips from three abdominoperineal resection specimens for each response) were mounted for isometric tension recording in a perfused organ bath at 36°C Atropine (10^{-6} mol l^{-1}) and gaunethidine (3×10^{-6} mol l^{-1}) were present throughout to inhibit cholinergic and adrenergic neurotransmission. Tone was established by loading the strips with the equivalent of a 1 g weight, but increased spontaneously thereafter. In this state, stimulation of the NANC inhibitory nerves (10 V, 0·5 ms duration, 8–20 pulses s^{-1}) produced relaxations sensitive to tetrodotoxin (3×10^{-6} mol l^{-1}). Sodium nitroprusside, which acts by liberating nitric oxide, also relaxed IAS strips in a concentration-dependent manner (10^{-8} to 5×10^{-6} mol l^{-1}). The inhibitory NANC responses were diminished by antagonists of nitric oxide synthase, partially diminished by 5×10^{-5} mol l^{-1} L-*N*-monomethylarginine (L-NMMA) (mean(s.d.) 73·4(3·3) per cent of original NANC relaxation, $P < 0·05$, Student's unpaired *t* test) but abolished by L-nitroarginine (L-NOARG) at the same concentration. The effects of L-NMMA and L-NOARG were competitively reversed by increasing concentrations of L-arginine (5×10^{-5} to 10^{-4} mol l^{-1}), but not its stereoisomer, D-arginine D-NMMA had no effect on the tissue Oxyhaemoglobin (5×10^{-5} mol l^{-1}), which scavenges endogenous nitric oxide, also abolished the relaxations.

These results suggest that nitric oxide is, or is very closely associated with, the neurotransmitter responsible for NANC nerve-mediated relaxations of the human IAS, and raise the possibility of specific pharmacological manipulation of sphincter activity

P15E expression in colorectal cancer

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Experimentally, tumour cells have been shown to suppress antitumour immune responses. *In vitro* experiments have suggested that this suppression is mediated via the secretion of a soluble suppressor factor, but attempts to demonstrate such factors in fresh tumours have proven difficult to conduct. One candidate for this suppressive moiety is the retroviral protein P15E, which is responsible for the immunosuppression induced by human retroviruses and has been discovered in several animal tumours. Antisense probes complementary to the known sequence of the P15E gene were made and used in Northern blots to examine messenger RNA (mRNA) from 22 fresh surgical specimens of colorectal cancers and histologically normal distant mucosa. The frequency of expression of mRNA for P15E in these tissues was as follows:

	P15E mRNA positive	P15E mRNA negative
Colorectal cancer	18 of 22	4 of 22
Normal mucosa	2 of 15	13 of 15

Thus, mRNA for P15E was identified more frequently in the tumours than in the normal mucosa ($\chi^2 = 14·2$, $P < 0·0001$). To confirm that the peptides coded for by these nucleotides were immunosuppressive, two peptides (FG10 and FG17) were synthesized corresponding to the sequences of the antisense probes and added to *in vitro* assays of the immune response (lymphocyte proliferation in response to the anti-CD3 antibody and the mixed lymphocyte reaction) with the following results·

	[^{3}H]thymidine uptake (c.p.m.)		
	Control	10^{-6} M FG10	10^{-6} M FG17
Anti-CD3	38 275(8916)	15 939(1898)*	14 023(1647)*
Mixed lymphocyte reaction	18 412(3323)	10 191(569)*	12 662(629)*

Values are mean(s.d.); $n = 5$. *$P < 0·05$ *versus* controls (Student's *t* test)

These data show that human colorectal cancer expresses mRNA for a potently immunosuppressive peptide This may be a target for future therapeutic strategies.

Effect of timing of radiotherapy on anastomotic wound healing of the cervical oesophagus

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Adjuvant radiotherapy after surgery confers a survival advantage in carcinoma of the upper aerodigestive tract. Recent studies suggest that a shorter interval may be preferable to the standard 4–6-week interval currently favoured, but the optimum time in terms of wound healing is unknown. A study was undertaken to determine the effect of timing of radiotherapy after surgery on wound healing of the upper oesophagus in a rodent model.

A transverse incision through half of the oesophageal circumference was repaired using three interrupted 6/0 Prolene (Ethicon) sutures in female Wistar rats. Radiotherapy (37·5 Gy) was delivered to the cervical oesophagus in the treated groups ($n = 18$) at 1 week (group 1), 3 weeks (group 2) and 6 weeks (group 3). Studies were performed 1 week after radiotherapy. Healing was assessed by clinical criteria, histological scoring and bursting strength, and compared with control groups each of 13 rats at similar intervals.

	Bursting pressure (mmHg)		Histological score	
Group	Treated	Controls	Treated	Controls
1	520(10·4)	540(12·3)	6·3(0·24)	0·76(0·20)*
2	510(12·2)	552(11·6)	6·1(0·17)	0·38(0·14)*
3	575(13·2)	554(12·1)	5·5(0·13)	0·33(0·14)*

Values are mean(s.e.m.). *$P < 0·001$ (Wilcoxon rank sum test)

Radiation changes of epithelial inflammation and necrosis were similar in the treated groups. Free perforation occurred in two animals in group 1 and two in group 2. No difference in bursting strength was detected between treated groups and controls. Wound healing was similar regardless of radiation timing. These results suggest that shortening the time interval between surgery and radiotherapy may not have a detrimental effect on anastomotic healing.

p53 mutation is an early event in transformation from metaplasia to neoplasia in Barrett's oesophagus

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Intestinal-type Barrett's oesophagus (CLO) predisposes to dysplasia and adenocarcinoma of the oesophagus. p53 is a nuclear phosphoprotein product of a gene which is normally undetectable by immunocytochemistry using conventional techniques because of its short half-life. Abnormalities of the p53 gene are common in a range of different neoplasms and may be due either to missense mutation and production of a mutant, or to allelic deletion.

Using a polyclonal antiserum CM-1 raised to recombinant human p53, the expression of p53 in the metaplasia–neoplasia sequence of CLO was investigated using 65 histological blocks from eight cases of intestinal CLO, seven cases of dysplastic CLO and seven cases of adenocarcinoma arising in CLO.

p53 immunoreactivity is not detectable in normal oesophageal epithelium or stroma, but was present in the nuclei of epithelial cells in six of eight cases showing metaplasia, in four of seven cases with dysplasia (both low and high grade) and in five of the seven adenocarcinomas, including in areas of *in situ* disease. There was, however, considerable variation in the number of p53 immunoreactive cells.

It is concluded that p53 expression is a common abnormality in CLO and its complications and appears to be a relatively early event. This strongly suggests that mutation of p53 (which is tightly linked with abnormalities of p53 expression) is a molecular event underpinning neoplasia in Barrett's oesophagus.

Central neuropeptide Y increases basal acid by decreasing central adrenergic inhibition of acid

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Intracerebroventricular (ICV) neuropeptide Y (NPY) increases basal acid output in dogs. ICV yohimbine, an α_2-adrenergic antagonist, also increases acid output in dogs, suggesting that there is tonic central α_2-adrenergic inhibition of acid secretion. In many neurones, NPY coexists with noradrenaline, suggesting that there may be functional interaction between the two neurotransmitters. In this study, the hypothesis that ICV NPY increases gastric acid secretion by decreasing central adrenergic inhibition of acid was examined.

Six dogs were prepared with gastric fistulae and chronic cerebroventricular guides that allowed intermittent cannulation of the lateral cerebral ventricle in the awake state. NPY_{13-36}, a presynaptic NPY receptor agonist, or $[\text{Leu}^{31},\text{Pro}^{34}]$NPY, a postsynaptic NPY receptor agonist, or control (0·1 per cent albumin in 0·9 per cent saline) was given by bolus ICV injection, and acid output recorded for 2 h. In separate studies, NPY (250 pmol kg^{-1}) was given 1 h either before or after desmethylimipramine or vehicle (consisting of polyethylene glycol 400 and 0·9 per cent saline) as control. Acid output was recorded for 2 h after the second injection.

NPY_{13-36} (1000 pmol kg^{-1}) significantly increased acid output (5·6(1·9) mmol per 2 h, $P < 0·05$) compared with control values (1·3(1) mmol per 2 h), whereas $[\text{Leu}^{31},\text{Pro}^{34}]$NPY (1000 pmol kg^{-1}) had no effect (1·1(1) mmol per 2h). The results of studies with NPY and desmethylimipramine are summarized in the *Table*

	Acid output (mmol per 2 h)
NPY then desmethylimipramine	9·9(2·9)
NPY then vehicle	8·9(4·1)
Vehicle then NPY	15·2(6·6)
Desmethylimipramine then NPY	3·5(1·2)*

*$P < 0·05$

The central stimulatory effect of NPY on acid is mediated at a presynaptic NPY receptor. Desmethylimipramine, which slows uptake of noradrenaline from the synaptic cleft, inhibits NPY-induced secretion when given before but not after ICV NPY. These studies suggest that ICV NPY may increase acid output by presynaptic inhibition of tonic release of noradrenaline in dogs.

Truncal *versus* highly selective vagotomy for duodenal ulcer: long-term results of a controlled trial

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In an era in which surgery for uncomplicated duodenal ulceration has become less commonplace, uncertainty persists concerning the optimal surgical procedure.

The aim of the present study was to compare the effectiveness and functional results of truncal vagotomy and pyloroplasty (TVP) and highly selective vagotomy (HSV), performed electively for uncomplicated duodenal ulceration. Patients with pyloric stenosis, or those requiring emergency surgery, were excluded.

Between 1973 and 1981, 193 patients with proven duodenal ulceration were included in the study. Patients were randomly allocated to undergo TVP ($n = 93$) or HSV ($n = 100$). The two groups were well matched for age and sex distribution. The operative time for HSV ranged from 88 to 140 (median 80) min, and for TVP from 35 to 100 (median 60) min ($P < 0·02$, Mann–Whitney U test). Patients were reviewed annually as outpatients. Postoperative follow-up ranged from 10 to 18 (median 16) years.

		Visick grade						H_2
Follow-up (years)	Trial group	1	2	3	4	Actuarial recurrence	Severe diarrhoea	blocker usage
5	HSV	35	44	16	5	8·1	3·6	3·6
	TVP	28	42	29	1	1·0	9·4	6·3
10	HSV	41	36	22	2	14·1	1·4	6·9
	TVP	28	33	34	5	4·2	9·1*	4·6
15	HSV	40	27	30	3	14·1	6·7	13·3
	TVP	26	38	31	5	7·4	12·8	5·1

Values are percentages. *$P = 0·04$ (two-tailed exact Fisher test)

There were no significant differences in proven recurrence rate (life-tables, log rank test), Visick grade, or use of H_2-receptor antagonists. There were late (over 10 year) recurrences after TVP but not HSV. The incidence of diarrhoea was significantly higher in the TVP group only at 10 years. These data fail to provide a strong preference for either type of vagotomy.

Erythromycin improves gastric emptying after oesophagectomy

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After oesophagectomy with cervical anastomosis, aspiration is described in over 10 per cent of patients and may be related to delayed gastric emptying Cisapride and erythromycin have both been shown to improve gastric emptying in the innervated stomach. Their effect on the postoesophagectomy stomach is unknown, but pyloroplasty is associated with additional anastomotic risks A 4-h study using 25 g technetium-99m tin colloid labelled egg white and 100 g indium-111 diethylenetriamine penta-acetate radiolabelled orange juice examined the rate of emptying of solids and liquids. Studies were carried out 2 months after three-stage oesophagectomy with preservation of the whole stomach in four different groups. Group 1 underwent resection without pyloroplasty and group 2 resection with pyloroplasty Group 3 was studied after 3 days of cisapride treatment, and group 4 after 3 days of erythromycin therapy.

Group	Procedure	*n*	Radiolabel remaining at 4 h (%)
1	Resection (no pyloroplasty)	16	56(6·8)
2	Resection with pyloroplasty	6	32(16·6)
3	Resection and cisapride	10	50(11·6)
4	Resection and erythromycin	6	18(9·2)*

Values are mean(s.e.m.) $*P = 0{\cdot}01$ (Mann–Whitney *U* test)

Neither cisapride nor pyloroplasty improved emptying of the postoesophagectomy stomach. Erythromycin provided a significant improvement in the rate of gastric emptying and may have a role in the treatment of problems due to gastric stasis after oesophagectomy.

Host cell infiltration of graft tissues in a non-rejecting model of small bowel transplantation

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Previous studies have demonstrated extensive host cell infiltration of graft tissues in rejecting small bowel allografts. However, immunohistological monitoring of small bowel transplantation is hampered by physiological trafficking of lymphocytes.

The present study assessed host cell infiltration of graft tissue in the absence of an allogeneic stimulus to the recipient A semiallogeneic non-rejecting model of rat small bowel transplantation was established by transplanting small bowel from DA rats into (DA x PVG) F_1 recipients. Host cell infiltration of graft mesenteric lymph node, Peyer's patch, lamina propria and intraepithelial compartment was assessed on days 1–8 by immunohistological staining using strain-specific monoclonal antibodies Infiltrating cells were counted and expressed as a percentage of the total cell number

	Graft tissue infiltration by host cells (%)			
Day	Mesenteric lymph node	Peyer's patch	Lamina propria	Intraepithelial compartment
1–2	19·3*	7·8*	1·8	0
3–4	91·6†	67·0†	9·9	0
5–6	56·0†	25·0	20·0	0
7–8	25·0†	32·0†	2·4	0

$*P < 0{\cdot}05$; $\dagger P < 0{\cdot}01$ *versus* lamina propria

Host cells preferentially infiltrated organized lymphoid tissues (mesenteric lymph node and Peyer's patch) compared with lamina propria In previous studies, rejecting small bowel allografts have shown infiltration of the intraepithelial compartment; no such infiltration was observed in this non-rejecting model.

In summary, this study has demonstrated host cell infiltration of graft tissues in the absence of an allogeneic stimulus, suggesting that histological identification of host cells in graft lymphoid tissue may not indicate rejection. However, the presence of host cells in the intraepithelial compartment may provide a more accurate indicator of rejection.

Endoscopic balloon dilatation of the pylorus

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Endoscopic balloon dilatation has been employed as the first-line management of benign peptic pyloric stenosis.

Thirty-one patients (23 men) presented with symptoms of peptic pyloric stenosis. The diagnosis was confirmed radiologically, and by the failure of a 9-mm endoscope to pass through the obstruction. The patient was sedated and dilatation performed using a through-the-scope technique. Under radiographic screening, the balloon was positioned through the stricture and inflated After the balloon was completely distended it was kept in place for 3 min. The procedure was repeated until the stricture was dilated to 15 mm. Successful dilatation was recorded as the passage of a 12·8-mm endoscope through the stricture. Nineteen patients underwent one dilatation, two patients two dilatations and nine patients three dilatations. The patients were then put on medical treatment with H_2 blockers.

One stricture could not be negotiated, and one patient after rapid restenosis was found on serial biopsy to have pyloric adenocarcinoma. Three patients suffered duodenal perforation during dilatation. Nine patients failed to gain symptomatic relief despite adequate dilatation and required surgery. Three patients developed a perforated duodenal ulcer, 3, 12 and 20 months after successful dilatation. Fourteen patients are asymptomatic with a median follow-up of 24 (range 12–48) months.

Peptic pyloric stenosis can be relieved in up to 60 per cent of patients by balloon dilatation. However, it carries a perforation rate of 10 per cent. Because of the continued ulcer diathesis, 12 patients required surgery for complications of ulcer disease (reobstruction or perforation). Endoscopic balloon dilatation cannot be recommended as first-line treatment for peptic pyloric stenosis

Factors influencing restitution of mammalian gastric mucosa *in vitro*

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Restitution is the process whereby intestinal mucosa is repaired after superficial damage The factors influencing this process have been extensively investigated in the amphibian. The aim of this study was to explore conditions that might influence restitution in mammalian gastric mucosa.

Ussing chambered rat gastric mucosa was injured by exposure of the luminal surface to 0·75 mol l^{-1} NaCl for 10 min. After washout of the saline, the tissue was allowed to recover with varying nutrient solutions at luminal pH 5. Continuous measurement of transmucosal potential difference (PD) and intermittent calculation of tissue resistance was undertaken

When 10^{-5} mmol l^{-1} colchicine was added to the nutrient solution, mean(s.e.m.) PD 70 min after injury reached 10·60(1·42) mV and mean(s.e.m.) resistance (*R*) 66·0(7·30) ohm cm^{-2} ($n = 5$). This recovery was no different from that of control tissues (PD 12·66(1·69), *R* 79·5(8·04), $n = 5$, *P* not significant).

Restitution at 70 min in the presence of 10^{-4} mmol l^{-1} cytochalasin B added to the nutrient solution (PD 5·35(1·27)) was significantly inhibited compared with controls (PD 13·35(1·65), $n = 5$, $P < 0{\cdot}05$).

Recovery at 70 min was also significantly inhibited by chelation of nutrient calcium with 4 mmol l^{-1} ethylenediamine tetra-acetic acid (PD 3·07(0·64), *R* 38·33(3·07), $n = 6$) compared with controls (PD 12·6(1·69), *R* 79·5(8·04), $n = 10$, $P < 0{\cdot}05$)

Histological evaluation of tissues removed from the chambers confirmed inhibition of restitution by cytochalasin B and chelation of nutrient calcium

This study confirms that restitution in mammalian gastric mucosa is not a function of cell division but is related to microfilament function. It is also a calcium-dependent process. Restitution is an important repair mechanism in mammalian gastrointestinal mucosa, and pharmacological manipulation of intramucosal conditions may have clinical implications.

Comparison of the anticarcinoembryonic antigen monoclonal antibody A5B7 and its Fab'2 fragment in intraoperative detection of colorectal cancer

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It has been suggested that specific localization of colorectal cancer may be improved with the use of monoclonal Fab'2 fragments directed against colorectal cancer antigens. This study prospectively analysed 25 patients with colorectal cancer who were randomized to receive either intact ^{125}I-radiolabelled anticarcinoembryonic antigen (CEA) monoclonal antibody (A5B7) ($n = 11$) or its Fab'2 fragment ($n = 14$). Peroperative localization of labelled antibody was achieved using a hand-held cadmium telluride probe.

The rate of clearance of both antibodies to achieve reasonable background levels was similar. The mean precordial count at operation (mean 14·5 days) was 25 per 2 s for A5B7 and 20 per 2 s for Fab'2. The mean(s.d.) tumour:normal colon ratios *in vivo* ($\geqslant 2 \cdot 1$ regarded as significant) were 3·3.1(2·1) for A5B7 and 5·7.1(3·1) for Fab'2. *Ex vivo* counts were 7·2·1(3·8) for A5B7 and 11·5·1(6·3) for Fab'2 (P not significant).

There was no significant difference between the mean percentage injected dose per kilogram achieved in tumour, blood or normal tissue for either intact A5B7 or its Fab'2 fragment. The mean(s.d.) tumour:blood percentage injected dose per kilogram ratio was 9·5(7·7) for A5B7 and 6·4(3·7) for Fab'2. The mean tumour:normal colon percentage injected dose per kilogram ratio was 4·5:1(2·8) for A5B7 and 3·1:1(2·1) for Fab'2.

Seventy-two lymph nodes were studied *ex vivo* (A5B7 $n = 29$, Fab'2 $n = 43$) and probe counts correlated with histology. Intact antibody accurately predicted nodal histology in 26 of 29 cases (90 per cent), and Fab'2 accurately predicted nodal histology in 35 of 43 (81 per cent) ($\chi^2 = 0 \cdot 91$, P not significant). Human antimouse antibody reaction was positive in four of ten cases for A5B7 and one of five cases for Fab'2. It is concluded that Fab'2 fragments may be used with safety and with equal efficiency to that of the intact antibody for intraoperative localization of colorectal cancer.

Delta F508 cystic fibrosis gene deletion protects against colonic and breast cancer

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It is known that the delta phenylalanine (F) 508 codon deletion in the cystic fibrosis gene protects against the development of malignant melanoma but not acute myeloid leukaemia[1]. This study examined the delta F508 status in three common solid tumours. DNA was extracted from buccal washes or paraffin-fixed tissue. The region around codon 508 was then amplified using the polymerase chain reaction, and normal and mutant alleles were detected using polyacrylamide gel electrophoresis.

The national carrier frequency for the delta F508 deletion has been estimated at one in 27. In our random control population of 228 people there were ten carriers, a rate of one in 23. In the 166 patients with a colonic tumour, a single carrier was identified ($P < 0 \cdot 05$ *versus* control). In 103 patients with breast cancer, only one carrier was identified. The carrier rate was normal (two in 58) in the prostate cancer patients.

Delta F508 deletion protects against the development of colon and breast cancer in addition to malignant melanoma. This broad-based protective function of the cystic fibrosis gene may explain the higher carrier frequency of the gene in many populations.

1. Warren N, Holmes J, Al-Jader L *et al.* Frequency of carriers of cystic fibrosis gene among patients with myeloid malignancy and melanoma. *Br Med J* 1991, **302**: 760–1.

Carcinogens in bile: results of a bioassay

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Many carcinogens bind with single DNA bases to form DNA adducts. This property allows DNA adducts to be regarded as markers of carcinogen exposure. Thus, the observation that significantly more adducts are present in the duodenal mucosa of patients with familial adenomatous polyposis (FAP) than in the duodenal mucosa of controls suggests either that FAP bile contains more carcinogens than does control bile, or that FAP mucosal DNA repair mechanisms are defective. To determine which of these two explanations is correct, a bioassay, with Home Office approval, was performed.

Gallbladder bile was aspirated at surgery from 13 FAP patients (seven women, six men, mean (range) age 34 (14–54) years) and from 14 control patients (nine women, five men, mean (range) age 49 (21–77) years). Bile was combined to make up an FAP pool and a control pool. FAP bile was given by gavage to one group of Fischer rats, and control bile to another group (seven rats per group, dose 0·5 ml bile per 100 g body-weight, thrice weekly for 9 weeks). Rats were killed at 1 year and samples of proximal small bowel were taken, snap-frozen and stored at −70°C until analysis. DNA was extracted from the small bowel samples and DNA adduct labelling was measured in triplicate by ^{32}P-postlabelling using thin layer chromatography.

Median (range) DNA adduct labelling was significantly greater in rats treated with FAP bile than in those treated with control bile (FAP bile 20 (11–38), control bile 11 (4–16) adducts per 10^9 nucleotides; $P = 0 \cdot 003$, Mann–Whitney U test).

These results suggest that adduct labelling is greatest in the FAP duodenum because more carcinogens are present in the bile of FAP patients than in the bile of control patients.

Survival after hepatic cryotherapy for hepatic metastases

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This unit has previously reported an encouraging experimental model, a clinical tumour marker and radiological data on hepatic cryotherapy. Ultrasonographically controlled hepatic cryotherapy has been used to treat 32 patients with irresectable hepatic tumours (28 colorectal cancer, one clear cell tumour, one melanoma, one ovarian tumour, one primary liver cancer). Two of these patients were treated twice. In 25 patients, a subcutaneous reservoir and hepatic arterial catheter was placed for monthly chemotherapy. This consists of folinic acid 50 mg bolus followed by an infusion of 5-fluorouracil 4 g over 4 days. One to ten metastases (median three) were treated per patient. Operations lasted from 2 h 15 min to 6 h 30 min (median 3 h 45 min). Fifteen patients required blood transfusion of 2–5 (median 3) units of packed cells. There was no perioperative mortality, liver abscess, bile leak or wound infection. The study looked at length of carcinoembryonic antigen (CEA) suppression after cryotherapy in 16 patients who received no chemotherapy, and the patients in this current series who did receive chemotherapy. In the group not receiving chemotherapy, CEA level had returned to the preoperative value by 3 months in five of eight patients, and by 6 months in six of eight patients. In those receiving chemotherapy, CEA had returned to pretreatment levels by 3 months in two of 11 patients and by 6 months in two of six patients. Patients fell into three categories: group 1, resectable lesions but unfit (three patients); group 2, irresectable lesions but four or fewer metastases (21 patients); and group 3, more than four lesions (eight patients). Six patients have died since operation (four from group 3 died at 2, 4, 7 and 12 months after operation, and two from group 2 died at 4 and 8 months after operation). Overall survival rates were 96 per cent at 3 months, 70 per cent at 6 months, 64 per cent at 9 months and 50 per cent at 12 months. In group 1, all patients are alive at 1, 10 and 15 months. In group 2, survival is 15 of 15 at 3 months, 11 of 12 at 6 months, four of six at 9 months and four of six at 12 months. In group 3, survival is seven of eight at 3 months, four of six at 6 months, two of five at 9 months, and the longest survivor died at 12 months. The median fall in CEA values after operation in group 2 patients was 92 (range 0–97) per cent and in group 3 patients 50 (range 0–76) per cent. These results are encouraging, particularly for patients in groups 1 and 2, who otherwise have few treatment options.

High-energy extracorporeal shockwave thermotherapy

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High-intensity shockwaves (HISWs) can produce rapid and intense tissue heating. A novel device (EDAP Pyrotech) capable of simultaneous shockwave generation, focusing and extracorporeal delivery, with imaging of the proposed target, was studied. Shockwaves are generated by piezoelectric crystals, and target a focal point of 10 × 2 mm. Simultaneous ultrasonographic imaging permits accurate targeting and detection of tissue combustion and vacuolization *In vitro* studies of a polyurethane target demonstrated temperature rises in excess of 300°C at the focal point. In a preliminary study, three groups of Landrace pigs received HISWs to discrete points on the liver parenchyma.

Group	No. of shockwaves	Time of killing
1 ($n = 4$)	30	48 h
2 ($n = 4$)	30	1 week
3 ($n = 4$)	30	2 months

There was no mortality in any group. Cardiovascular monitoring revealed that HISWs did not induce any haemodynamic changes during treatment and that core temperatures and liver function tests were unaffected by this therapy. Ultrasonographic monitoring during treatment demonstrated discrete hyperechoic areas with acoustic shadowing suggesting cavitation. Animals in groups 1 and 2 demonstrated discrete necrotic cylinders within the liver in all cases with a mean(s.d.) diameter of 2(0·21) cm. Histological examination revealed a pattern of necrosis and vascular changes suggestive of an ischaemic role in these changes. In addition, there were areas of coagulative necrosis consistent with thermal injury Other findings included focal fibrinoid necrosis of arterioles, venules and bile ducts. There was a sharp demarcation between burnt tissue and adjacent liver parenchyma. In animals in group 3 the necrotic cavities had become surrounded by mature fibrosis. These early results indicate that high-energy shockwaves delivered extracorporeally can cause specific destruction of liver tissue by focused hyperthermia and cavitation. Clinical studies of this device are required to asses the possible virtue of HISWs in the treatment of liver and other tumours.

Splanchnic vascular changes in response to intrahepatic and extrahepatic tumour

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The hepatic perfusion index (HPI), the ratio of hepatic artery to total liver blood flow, is increased in patients and animals with liver tumour. The aim of the present study was to investigate whether this change was specific to the presence of tumour within the liver.

A three-limbed reference microsphere experiment was performed, comparing the splanchnic blood flow in rats with HSN sarcoma implanted in the liver or the flank and in sham operated animals.

	Control	Flank tumour	Hepatic tumour
Hepatic arterial flow (ml min^{-1} g^{-1})	0·113 (0·09–0·17)	0·069 (0·05–0·15)	0·127 (0·09–0·16)*
Splanchnic flow (ml min^{-1} g^{-1})	0·835 (0·53–0·98)	0·477 (0·29–0·76)	0·545 (0·47–0·66)
Calculated HPI	0·077 (0·06–0·09)	0·078 (0·07–0·10)	0·128 (0·11–0·23)*†

Values are median (range) $^*P < 0·05$ *versus* flank tumour, $†P < 0·01$ *versus* controls (Kruskal–Wallis rank sum test)

Hepatic arterial flow per gram of liver was similar in the intrahepatic tumour and sham operated groups, but was less in those with extrahepatic tumour. Splanchnic flow was reduced in both animals with hepatic tumour and those with flank tumour, compared with controls. The HPI was significantly greater in animals with intrahepatic tumour than in the other two groups.

This study suggests that the change in HPI is dependent on intrahepatic tumour and may be due to local protection of the hepatic artery against the action of a circulating vasoactive agent.

Prevention of cutaneous phototoxicity after photodynamic therapy

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The most troublesome side-effect of photodynamic therapy is skin photosensitivity, which lasts up to 8 weeks. Exposure to sunlight leads to cutaneous phototoxicity with manifestations similar to those of sunburn. The effect of antihistamines (ranitidine and terfenadine) and thromboxane inhibitors (aspirin and indomethacin) on skin photosensitivity was investigated using the murine ear swelling response model, which provides a quantitative measurement of the phototoxic response. Control and study groups of BALB/c mice (five each) were photosensitized with photofrin by intraperitoneal injection, and 5 days later were irradiated with solar simulated light at 5 and 15 J cm^{-2} Study groups received the drugs 2 h before irradiation. The changes in ear thickness before and after irradiation at various times up to 144 h were measured. In the control group at 5 J cm^{-2} there was an immediate phototoxic response which peaked at 1 h whereas at 15 J cm^{-2} the response was biphasic with peaks at 1 and 48 h.

	Net increase in ear thickness (mm × 10^{-3})		
	5 J cm^{-2}	15 J cm^{-2}	
	1 h	1 h	48 h
Control	111(4·83)	111·2(3·37)	137(7·58)
Ranitidine	70(3·19)*	77·2(3·40)	58·6(11·35)*
Terfenadine	105·2(1·39)	115·8(2·85)	162(4·76)
Ranitidine and terfenadine	92·2(6·41)	115·6(2·69)	164·6(4·01)
Aspirin	66(3·03)	70·8(2·54)	42·8(2·87)*
Indomethacin	61·4(1·96)*	73·2(4·31)*	25·2(3·93)*
Aspirin and indomethacin	62·4(1·86)*	69·5(6·20)*	34(5·58)*
Ranitidine and indomethacin	67·4(4·40)*	61·2(4·73)*	19·2(1·20)*

Values are mean(s.e.m.). $^*P < 0·001$ (Student's t test)

These data suggest that ranitidine, aspirin and indomethacin reduce cutaneous phototoxicity in mice, especially the delayed response.

Cimetidine acts via histamine receptors to inhibit the growth of human colonic cancer

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This study investigated whether cimetidine will inhibit the growth of human colonic cancer in an animal model, and related this effect to the presence of histamine receptors. Ethical committee approval was obtained. Four human colonic cancer cell lines were grown as xenografts in 20 nude mice. Ten were administered oral cimetidine at a dose of 100 mg kg^{-1} day^{-1} and ten served as controls Tumour diameters were measured 3 times a week. After 28 days, the mean tumour diameters in the treated groups were less than those in controls by 10–30 per cent. Using ANOVA, there was a significant inhibition in growth for the cell lines LoVo, LIM2412 and C170 ($P < 0·05$), but the inhibition was not statistically significant in LIM2405 ($P = 0·89$) These cell lines were then assayed for histamine receptors by incubating cell suspensions with histamine, labelled with fluorescein, at a concentration of 10^{-5} mol l^{-1}. Cellular binding was determined by flow cytometry. Binding was found to be saturable by 45 min at 37°C, and to dissociate by 45 min after washing. Non-specific binding, determined by cellular fluorescence after addition of 1000-fold excess of unlabelled histamine, was 15 per cent of total binding for all cell lines. The C_{150} for unlabelled histamine, when added to the solution, was 5×10^{-4} mol l^{-1}; for cimetidine it was 5×10^{-3} mol l^{-1}, and for diphenhydramine $> 10^{-2}$ mol l^{-1} Mean(s.d.) levels of specific binding, using arbitrary units of fluorescence, were: LoVo, 4000(400); LIM2412, 2500(300); C170, 2400(300); LIM2405, 1500(300); and normal lymphocytes, 300(15). These results suggest that colonic cancer cell lines possess a high concentration of histamine receptors, predominantly H_2 in type, and that a higher concentration of H_2 receptors correlates with an *in vivo* tumour response to the H_2 antagonist cimetidine.

Genetic fingerprinting of breast lesions

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The digestion of DNA by a standard restriction enzyme provides hypervariable sequences which produce a pattern, or genetic fingerprint, unique to each individual. The genetic fingerprint pattern of DNA extracted from every nucleated cell from any organ or tissue in one person should be exactly the same. Thus, differences between the genetic fingerprints of DNA isolated from a breast tumour and from a patient's normal cells would indicate chromosomal rearrangement and consequently could be used as a marker of malignant change.

Constitutional and tumour DNA from 80 patients with a spectrum of breast lesions were subjected to genetic fingerprinting analyses. The restriction enzyme HaeIII and the radiolabelled minisatellite probes 33.15 and 33.6 were used For the 65 invasive cancers assessed, genetic fingerprint analysis was found to be more sensitive than DNA ploidy but independent of nodal status.

Histological diagnosis	*n*	No of cases with fingerprint changes
Benign lesion	10	1 (10)
Carcinoma *in situ*	5	2 (40)
Invasive cancer		
Grade I	17	8 (47)
Grade II	24	15 (62)
Grade III	24	15 (62)

Values in parentheses are percentages

Nearly 60 per cent of invasive breast tumours examined had one or more alterations in their genetic fingerprint pattern. Further development of this method for detection of minimal changes in DNA may allow for the distinction between normal and malignant cells, especially in borderline cases (atypical hyperplasia, carcinoma *in situ*)

Analysis of the human progesterone receptor gene in breast carcinoma: identification of patients at risk

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Long-term survival in patients with breast carcinoma remains suboptimal and identification of patients a risk of breast cancer remains an unrealized goal Isolation of a complementary DNA (cDNA) probe (hPR-1) for the human progesterone receptor (PR) gene in this laboratory provided us with a molecular probe for detection of alterations in the PR gene. A 1·85-kilobase (kb) fragment encoding the DNA-binding and hormone-binding domain of human PR was used to analyse DNA from human blood and breast tissue. Genomic DNA was prepared from breast tumour tissue from 47 patients with primary breast cancer and peripheral leucocytes from 42 breast cancer patients, digested by the restriction enzyme TaqI, and subjected to Southern blotting. In eight of 42 blood samples and 11 of 47 breast tumours a distinct 1·9-kb restriction fragment length polymorphism (RFLP) was detected. None of the 40 control blood samples displayed this RFLP pattern, suggesting that this is a germ line anomaly in these patients and not a mutation in tumour DNA. Amplification of the c-*erb*B2 oncogene was found in seven of 47 tumours, but in only one of the group who displayed the 1·9-kb RFLP. These data suggest that human PR gene analysis with hPR-1 cDNA and TaqI digestion offers a potential means of identifying people at risk of developing breast carcinoma.

Breast carcinoma cells expressing epidermal growth factor receptor: a target for monoclonal antibody therapy

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In recent years monoclonal antibodies (Mabs) reacting with tumour-associated antigens have attracted considerable interest as potential immunotherapeutic agents Transforming growth factor alpha (TGF-α) acting via the epidermal growth factor receptor (EGF-R) has been suggested to function as an autocrine growth factor in the progression of many different cancers to the metastatic stage. This study characterized non-immunological antitumour effects of Mab425, which binds to EGF-R, on the breast cancer cell line BT-20 Direct radioimmunoassays (^{125}I) were performed using human EGF and Mab425 to determine the number of EGF-R present on the line. Anchorage-independent growth assays for the detection of TGF-α-like activity in spent media of the BT-20 cell line were carried out using the NRK soft agar assay. Stimulation growth assays were performed on the cell line by adding TGF-α to cells seeded in 24-well culture plates Similarly, growth inhibition assays were carried out by adding Mab425 at different concentrations and determining cell counts at days 1 and 14 after seeding, using a Coulter cell counter.

	BT-20
EGF molecules bound per cell	$1{\cdot}2 \times 10^6$
TGF-α secretion (ng ml^{-1})	4·6
Inhibition with Mab425 (%)	41

Mab425 was found to inhibit significantly growth of the breast cancer cell line BT-20. This correlated with the fact that this cell line secreted detectable levels of TGF-α, expressed a high number of EGF-R, and also responded to exogenously added TGF-α in standard growth stimulatory assays (not shown). This study demonstrates that, in addition to immunological antitumour effects, Mab425 may have a dual, possibly synergistic, effect on tumour cells expressing EGF-R in patients with breast cancer.

Tamoxifen treatment for breast cancer in elderly patients

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In 1984 a trial was launched to evaluate the role of surgery in women over the age of 70 presenting with operable breast cancer and treated with tamoxifen Although about 30 per cent of breast cancers occur in elderly women, current studies report contradictory results when comparing primary management by surgery alone (S), tamoxifen alone (T), or tamoxifen plus surgery (TS).

To date, 446 patients have been randomized into this multicentre trial. Of these, 434 were available for the latest analysis (the remaining 12 were entered after the analysis cut-off date) with a median follow-up of 3·5 years The trial's main endpoints were time to change of management, and overall survival. At this time, 44 changes of management (20·8 per cent) have occurred in the TS group ($n = 212$) compared with 101 of 222 (45·5 per cent) in the T group, which is statistically significant ($\chi^2 = 31{\cdot}72$, $P < 0{\cdot}0001$, relative risk 0·38, 95 per cent confidence interval 0·27–0·53) This means that, of those who have reached 2 years, almost 50 per cent on tamoxifen alone have undergone a change of management, with about 65 per cent of such patients ($n = 65$) having received surgery by 2 years after diagnosis Conversely, about 50 per cent of patients who received tamoxifen alone have not undergone a change of management by 2 years. With regards to overall survival, 65 of 222 patients in the T group (29·3 per cent) have died compared with 44 of 212 (20·8 per cent) in the TS group This just reaches statistical significance in favour of the TS group ($\chi^2 = 3{\cdot}9$, $P = 0{\cdot}048$, relative risk 0·69, 95 per cent confidence interval 0·47–1·0).

Do these data finally resolve the issue as to whether elderly patients presenting with operable breast cancer should be recommended immediate surgery, or just be given tamoxifen which may adequately control the disease?

Bile acids induce oestrogen-regulated proteins in MCF-7 human breast cancer cells

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Bile acids may have carcinogenic properties and/or growth-promoting effects on human adenocarcinomas. The major circulating bile acid, glycochenodeoxycholic acid (GCDC), down-regulates oestrogen receptor and induces progesterone receptor (PR) in MCF-7 breast cancer cells to a similar extent to 10 nmol l^{-1} oestradiol. The present paper reports the effects of GCDC and chenodeoxycholic acid (CDC) on two secreted proteins which are also regulated by oestrogens, namely pS2 and procathepsin D.

GCDC (10 and 50 μmol l^{-1}), CDC (10 μmol l^{-1}), oestradiol (10 nmol l^{-1}) or carrier alone (0·1 per cent ethanol, control) in phenol red free DME/F12 medium containing 1 $\mu g\,ml^{-1}$ insulin and 5 per cent oestrogen and bile acid stripped fetal calf serum were added to 10^6 preconditioned MCF-7 cells 24 h after plating out in 75 cm^2 plastic flasks. After 7 days the cells were harvested and washed, and whole cell extracts prepared by homogenization in 10 $mmol\,l^{-1}$ HEPES buffer containing 0·4 $mol\,l^{-1}$ KCl and assayed immediately for oestrogen receptor and PR by enzyme immunoassay (Abbott Diagnostics). Cell extracts and conditioned medium were stored at −40°C until assayed for pS2 and procathepsin D by radioimmunoassay

	Control	Oestradiol	GCDC 10 $\mu mol\,l^{-1}$	GCDC 50 $\mu mol\,l^{-1}$	CDC
pS2					
Cells (ng per mg protein)	44(13) (*n*=4)	159(18)* (*n*=4)	114(4)† (*n*=3)	131(15)* (*n*=4)	114(20)† (*n*=4)
Medium (ng per 10^6 cells per 24 h)	37(11) (*n*=4)	151 (*n*=1)	217(125) (*n*=2)	201(55) (*n*=4)	126(40) (*n*=3)
Procathepsin D					
Cells (pmol mg^{-1})	22(5) (*n*=6)	28(5) (*n*=5)	29(7) (*n*=4)	28(8) (*n*=6)	30(4) (*n*=4)
Medium (nmol per 10^6 cells per 24 h)	465(48) (*n*=2)	560 (*n*=1)	953(90) (*n*=2)	848(5) (*n*=2)	570 (*n*=1)

Values are mean(s.e.m.) $^*P < 0·01$, $^†P < 0·05$ (Dunnett test for multiple comparisons with control)

The effects of GCDC and CDC on oestrogen receptor and PR were as previously observed. The degree of induction of pS2 was similar to that seen for PR, although the changes in procathepsin D were relatively modest

The major serum bile acid, GCDC, appears to exhibit oestrogenic activity on several ostrogen-regulated proteins of MCF-7 cells and may influence growth and behaviour of breast cancer *in vivo*.

Ultrasonography in monitoring breast cancer response to primary adjuvant systemic treatment

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Clinical examination and mammography are currently the standard techniques for monitoring changes in breast tumours in response to primary systemic treatment Ultrasonography is an alternative technique which has not previously been evaluated in this context The aims of the present study were to assess the accuracy of ultrasonography in measuring tumour size, and to evaluate the efficacy of sequential ultrasonography in monitoring response to treatment.

Tumour size was measured in 63 consecutive patients with breast cancer, clinically, mammographically and by ultrasonography, in the week before surgery After surgery, tumour size was reported by the pathologist. Sequential tumour measurements were carried out in a further 25 patients undergoing primary systemic treatment.

In all, 52 measurements were assessable. Ultrasonographic measurements showed a strong linear correlation with actual tumour size ($r^2 = 0·91$, $P < 0·0001$). The relationship between actual size and clinical or mammographic size was log-linear, and the correlation was less good ($r^2 = 0·70$, $r^2 = 0·80$, respectively, $P < 0·0001$) Sequential ultrasonography correctly evaluated response in 23 of 25 cases, compared with 20 of 25 cases by clinical measurements and 15 of 25 by mammography

Ultrasonography provides a better estimate of tumour size compared with mammography or clinical examination. It is the technique most likely correctly to evaluate response to primary systemic treatment.

Axillary node status in women with screen-detected breast cancer

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With the development of the national breast screening programme an increasing number of patients with small breast tumours is being treated. The value of axillary surgery for these women has not yet been established.

Of 22 612 women undergoing breast screening, axillary node clearance has been undertaken in 113 women of 164 with a screen-detected invasive breast cancer (median age 60 (range 49–73) years) Lymph nodes were involved in 35 of 113 patients (31 per cent).

The presence of lymph node involvement was found to vary directly with the size of the invasive component, this being significantly larger within the node-positive group ($P < 0·0001$). Only one patient had nodal involvement with a tumour <10 mm in diameter.

Diameter of invasive component (mm)	Lymph nodes involved	Lymph nodes not involved
0–9	1	16
10–19	13	43
⩾20	21	19

We conclude that in women with screen-detected breast cancer the size of the invasive component of the primary breast tumour is a guide to the likelihood of lymph node involvement Axillary node clearance may be omitted in some postmenopausal women with breast cancers that have an invasive component <10 mm in maximum diameter.

Biological significance of microcalcification in breast cancer

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Mammographic microcalcification is a feature of many primary breast cancers. Extracellular free Ca^{2+} is vital in cellular adhesion, and intracellular Ca^{2+} is a regulator of many cell functions. The deposition of calcium salts in microcalcification may be of biological significance. The possible clinical significance of microcalcification in relation to metastasis formation was investigated by assessing tumour involvement of resected regional (axillary) lymph nodes in relation to mammographically detected microcalcification in the primary tumour in 94 consecutive patients undergoing surgery for breast cancer.

	Microcalcification in primary tumour	
	Present	Absent
Patients with positive nodes	13 (46)	18 (27)
Patients with negative nodes	15 (54)	48 (73)
Nodes involved	50 (24·3)	70 (13·7)
Nodes uninvolved	156 (75·7)	441 (86·3)

Values in parentheses are percentages

Significantly more nodes were involved with tumour (24·3 per cent) when microcalcification was present in the primary tumour than when it was absent (13·7 per cent; $P < 0·001$, χ^2 test). Of patients with microcalcification 46 per cent were node positive, 27 per cent with no microcalcification were node positive.

There was no significant difference between the two groups in primary tumour size (T_0, 11 per cent; T_1, 36 per cent; T_2, 43 per cent; T_3, 11 per cent in the group with microcalcification *versus* T_0, 6 per cent; T_1, 35 per cent; T_2, 58 per cent, T_3, 4 per cent in the group with no evidence of microcalcification) or mean age (63·8 *versus* 60·4 years in the respective groups).

Microcalcification is associated with an increased incidence of nodal metastasis and its presence may imply a biologically significant disorder of calcium metabolism.

Influence of endogenous prostaglandins on the action of peptides on gallbladder motility

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There is mounting evidence that endogenous prostaglandins play an important role in gallstone disease. Non-steroidal anti-inflammatory drugs will prevent gallstone formation in animals and possibly in humans, probably by inhibition of endogenous prostaglandin synthesis.

This study examined the influence of indomethacin on the action of gastrointestinal regulatory peptides in gallbladder motility. The aims were· to establish the character of the response in guinea-pig gallbladder *in vivo* to intravenous administration of increasing doses of cholecystokinin (CCK) and neurotensin (NT); and to investigate the effect that indomethacin has on this response. A perfused gallbladder model was used in anaesthetized guinea-pigs. All experiments were approved by the animals ethics committee

Dose–response experiments were performed in two groups of animals for CCK ($n = 8$) and NT ($n = 13$). Bolus intravenous injections of peptide were given every 30 min and intragallbladder pressure measured continuously Doses of CCK of 2, 20, 40 and 80 pmol kg^{-1} and 100, 200, 500, 1000 and 2000 pmol kg^{-1} NT were used. Gallbladder response to CCK ($n = 7$) and NT ($n = 6$) was assessed before and after treatment with indomethacin (2·5 mg kg^{-1}).

A characteristic response was seen for each peptide and both exhibited a dose–response phenomenon for change in intragallbladder pressure (CCK: $r = 0{\cdot}59$, $P < 0{\cdot}001$; NT: $r = 0{\cdot}54$, $P < 0{\cdot}001$). The response to CCK was unchanged by pretreatment with indomethacin but the response to NT decreased ($P < 0{\cdot}05$, Student's paired t test), and in some animals was abolished

From this study it is concluded that CCK and NT cause contraction of the guinea-pig gallbladder *in vivo* and pretreatment with indomethacin decreases the response to NT but not CCK, indicating that the action of NT on the guinea-pig gallbladder *in vivo* may be prostaglandin-dependent

Cholecystectomy and gastro-oesophageal reflux disease

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There is an increased incidence of gastro-oesophageal reflux in patients who have undergone cholecystectomy[1] A study, approved by the hospital ethics committee, was undertaken to determine prospectively whether cholecystectomy resulted in increased reflux and whether this was influenced by the type of operation Patients were studied before and 3 months after cholecystectomy using upper gastrointestinal endoscopy, gastric and oesophageal pH monitoring and oesophageal manometry. Group 1 patients underwent open cholecystectomy, group 2 laparoscopic cholecystectomy.

	Open cholecystectomy ($n = 30$)	Laparoscopic cholecystectomy ($n = 10$)
Acid reflux score (DeMeester)		
Before surgery	16·9(2·8)	16·1(5·0)
After surgery	33·7(7·0)*	34·4(5·8)*
Supine gastric pH >4 (percentage of time)		
Before surgery	7·7(2·8)	14·5(4·0)
After surgery	13·7(5·9)	17·1(5·0)
LOSP (mmHg)		
Before surgery	16·2(0·9)	13·8(0·1)
After surgery	15·3(1·2)	8·8(1·3)

Values are mean(s.e.m.) *$P < 0{\cdot}05$ (Wilcoxon's signed rank test)

Cholecystectomy resulted in increased gastro-oesophageal reflux regardless of operative technique Lower oesophageal sphincter pressure (LOSP) did not change significantly but there was a trend towards increased supine gastric alkalinization (suggesting duodeno-gastric reflux) which was not significant Neural and hormonal mechanisms may link these findings which have implications for patients with cholelithiasis and gastro-oesophageal reflux

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Effect of cholecystectomy on plasma cholecystokinin levels

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Cholecystokinin (CCK), in addition to its effect on gallbladder contraction, has a role in regulating gastrointestinal peristalsis. Intraduodenal bile acids exert a negative feedback control on CCK release. Cholecystectomy in dogs leads to increased CCK secretion, probably by abolishing the intermittent meal-stimulated bile salts inhibition. Studies in humans have been limited by difficulties in CCK assay.

With a new specific and sensitive radioimmunoassay plasma CCK was measured before and after a meal of 60 ml corn oil in mashed potato in normal controls, patients with symptomatic gallstones (GS), and patients after cholecystectomy (PC)

	Time after ingestion of corn oil (min)			
	Before	5	30	45
Controls ($n = 13$)	0·59(0·1)	0·87(0·13)	2·6(0·48)	1·9(0·34)
GS ($n = 14$)	1·1(0·23)	1·3(0·36)	3·6(1·6)	2·5(0·5)
PC ($n = 11$)	0·69(0·11)	1·95(0·89)*	4·74(0·87)*	4·69(0·86)†

Values are mean(s.e.m.) plasma CCK levels expressed in pmol l^{-1} *$P < 0{\cdot}05$ *versus* controls, †$P < 0{\cdot}02$ *versus* controls; $P < 0{\cdot}05$ *versus* GS (Mann–Whitney U test)

Fasting levels were similar between the groups but meal-stimulated levels were significantly raised following cholecystectomy, suggesting impaired feedback control. It is further suggested that these altered CCK levels may be responsible for the motility disturbances which are described following cholecystectomy.

Intraperitoneal aprotinin therapy and the clinical course of acute pancreatitis

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Fatal acute pancreatitis (AP) is usually associated with multisystem failure (MSF), MSF is readily initiated by agents formed within the inflammatory peritoneal exudate, the only site of uninhibited protease activity in AP. Continuous peritoneal lavage removes the toxic exudate but causes fluid sequestration, respiratory embarrassment and protein loss, and does not improve survival rates. Pharmacodynamic studies demonstrated that intermittent lavage, instilling 5×10^6 kallikrein inhibitor units intraperitoneal aprotinin (IPA) in 1000 ml saline, repeated 8 h later, abolishes intraperitoneal protease activity for 24 h without adverse effects. A prospective, controlled trial was undertaken in 21 hospitals, comparing the incidence of MSF, clinical course, length of stay and outcome (death or survival) from AP managed by standard conventional management *versus* IPA plus standard conventional management MSF was defined by predetermined criteria, and severity monitored by daily APACHE-II scores[1]

During a 4-year period, 710 patients with AP were assessed (369 men, 341 women; median age 57 (range 14–97) years). Causes were gallstones 34 per cent, alcohol 19 per cent. Patients were entered into the study if aged 16–84 years, with symptoms for <72 h and no contraindication to lavage or IPA, but those with obviously mild AP (no peritonism, hypoxia, hypotension) were excluded Of 208 patients randomized, three refused consent to lavage, two cannulations failed, leaving 96 IPA and 107 standard conventional management patients, of comparable age, sex, cause, Imrie score, and admission APACHE-II score.

Group	Fatal attacks*	MSF*	Median APACHE-II†			Median hospital stay (days)†
			0 h	24 h	48 h	
SCM only ($n = 107$)	19 (17·8)	15 (14·0)	8 (6–12)	9 (6–12)	8 (5–12)	12 (9–19)
IPA plus SCM ($n = 96$)	19 (19·8)	18 (18·8)	9 (6–11)	9 (5–11)	8 (5–11)	14 (10–16)

Values in parentheses are *percentages, †interquartile range SCM, standard conventional management

IPA resulted in no adverse events There were no significant differences in overall mortality rate, MSF incidence, MSF severity (daily APACHE-II scores 0–7 days) or hospital stay, even when attacks were stratified for severity using Imrie or admission APACHE-II scores Given the statistical power of the study, IPA does not appear to influence either the course or the overall outcome of AP.

1. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE-II· a severity of disease classification. *Crit Care Med* 1985; **13**: 818–29.

Marked placebo responses in chronic pancreatitis: final results of a controlled trial of Creon therapy

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Painful chronic pancreatitis frequently results in opiate dependency. Raised pancreatic intraductal pressure is often responsible for pain, but may be reduced through the duodenopancreatic negative feedback mechanism[1] Duodenal intraluminal trypsin inhibits cholecystokinin secretion, which reduces enzyme secretion, thus lowering pancreatic intraductal pressure. In a multicentre study, 78 patients with confirmed chronic pancreatitis, but without steatorrhoea, were randomized to receive 4 weeks of Creon (granulated pancreatin microspheres, three capsules four times daily), followed by 4 weeks of identical placebo capsules, or *vice versa* A 'rescue' analgesic (dihydrocodeine) was supplied The study was successfully completed by 65 patients: 40 men (mean age 47 years) and 25 women (mean age 53 years) A history of alcohol abuse was elicted from 29 men and seven women. Data collected from interviews and diaries to assess efficacy included pain severity score (scale 0–5), pain frequency/duration index, rescue analgesic consumption, overall clinical improvement, and patient preference. Bowel frequency and body-weight were also recorded.

Parameter	Before therapy	Placebo	Creon
Pain severity score	2·66(0·82)	2·05(0·93)‡	1·93(1·04)‡
Frequency/duration index	59·9(61·5)	36·5(45·7)†	32·0(47·8)†
Bowel frequency (day^{-1})	2·05(1·63)	1·67(1·17)*	1·53(1·05)*
Body-weight (kg)	63·3(14·6)	63·2(14·3)	63·0(14·2)

Values are mean(s.d.) *$P < 0{\cdot}05$; †$P < 0{\cdot}01$; ‡$P < 0{\cdot}001$ (*versus* before therapy, ANOVA)

Mean daily analgesia use was 51 mg during placebo treatment and 45 mg during Creon treatment (P not significant). During placebo, 31 patients felt improved, 20 felt unchanged and 14 felt worse, while during Creon treatment, 31 felt improved, 25 felt unchanged, and nine felt worse (P not significant, χ^2 test). Placebo was preferred by 24 patients, Creon by 29, and 12 expressed no preference (P not significant, χ^2 test). Trends in favour of Creon *versus* placebo were observed consistently and, although none was statistically significant, further evaluation may be warranted The significant placebo responses were notable, and have implications for other studies of medical or surgical treatments for this disease.

1. Ihse I, Lilja P, Lundquist I. Feedback regulation of pancreatic enzyme secretion by intestinal trypsin *Digestion* 1977, **15**: 303–8.

Coagulation, fibrinolysis and endothelial function in acute pancreatitis

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Parameters of coagulation, fibrinolysis and endothelial function were assessed in 18 patients with acute pancreatitis receiving intravenous C1 esterase inhibitor (C1-INH), antithrombin III (AT-III) and immunoglobulin G over a 7-day period. It was found that mean(s.d.) C1-INH levels were 92·9(15·5) on admission, rising significantly by 24 h to 240(83·9) ($P < 0{\cdot}001$, Student's paired t test) and remaining elevated by day 7 at 240(132) ($P < 0{\cdot}001$) in keeping with its administration Thrombin–antithrombin III complex levels (μg l^{-1}) were high on admission (19·1(16·5)) and tended towards normal by day 7 (9·1(8·8), $P < 0{\cdot}05$). This reflects increased generation of thrombin owing to tissue damage, which is then complexed with AT-III Plasminogen levels (percentages) were high on admission, at 92·5(18·2), falling at 24 h to 79·6(17·8) ($P < 0{\cdot}05$) and then rising towards normal by day 7 (86(18)), reflecting conversion of plasminogen to plasmin during the period of fibrin formation. Increased fibrinolytic activity was shown by high levels of fibrin degradation products (1288(388) ng ml^{-1} on admission) and tissue plasminogen activator (239·6(221·5) on admission). These remained elevated throughout the study period, although this was partly balanced by increased plasminogen activator inhibitor (PAI) levels (20·6(8·1) units ml^{-1} on admission) Increased PAI levels probably reflect widespread endothelial disruption; this is supported by elevated levels of factor VIII–von Willebrand factor antigen. Endothelial function was found to be markedly disrupted because of extremely high levels of PAI and factor VIII–von Willebrand factor antigen (310(97·8) on admission, 309·1(116·8) by day 7).

This study demonstrated a generalized activation of coagulation with a resultant increase in fibrinolysis and a concomitant severe vasculopathy in acute pancreatitis, which persisted beyond the 7-day period of study The data presented may indicate a role for endothelial protectors in this disease.

Basis for an autoimmune reaction in chronic pancreatitis

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The precise aetiology of chronic pancreatitis is unclear, but the frequent presence of mononuclear cells suggests involvement of a cell-mediated immune mechanism. Aberrant expression of major histocompatibility complexes (MHCs) is a prerequisite for organ-specific autoimmunity, and normal pancreatic epithelial cells do not express such complexes Expression of MHC class I (β_2-microglobulin) and class II (human leucocyte antigen (HLA)-DR) determinants and the presence of T lymphocytes (UCHL1) were investigated in 93 patients (64 men, 29 women; mean age 40·5 years) undergoing operation for chronic pancreatitis. Aetiological agents were alcohol abuse (63 patients), recurrent acute pancreatitis (12 patients), congenital lesions (two patients) and unknown (16 patients). Immunohistochemical staining of archival tissue sections involved standard immunoperoxidase techniques using specific antisera. No MHC expression was seen in ten histologically normal pancreatic specimens (controls). The expression of β_2-microglobulin in pancreatic epithelial cells was observed in 76 specimens (82 per cent) while HLA-DR was present in 48 (52 per cent). Staining of both MHC determinants was confined to ductular and ductal epithelium with no staining of acinar cells: β_2-microglobulin (ductules 63 per cent, ducts 51 per cent; P not significant) and HLA-DR (ductules 44 per cent, ducts 42 per cent; P not significant). Positive staining was not related to aetiological agent or age. T lymphocytes were much more prominent in chronic pancreatitis (mean(s.e.m.) 131(15) per high power field) than control specimens (5(1), $P < 0{\cdot}05$). This aberrant MHC expression, together with a marked T cell infiltration, suggests an immunological contribution to chronic pancreatitis.

Laparoscopic bilioenteric drainage in an experimental model

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A laparoscopic technique of cholecystojejunostomy using single-layer continuous deep seromuscular polyglactin 3/0 sutures was used in survival and non-survival experiments in a piglet model.

In five non-survival experiments, the anastomosis was patent in all five pigs, the degree of peritoneal contamination was absent or minimal, and a significant leak was demonstrated radiologically in only one of five animals. In six survival experiments, the anastomoses were assessed after 4 weeks at laparotomy by instillation of 50 ml isotonic saline into the gallbladder after clamping the cystic duct. Five of six pigs had a patent anastomosis for rapid drainage of the fluid bolus. Minimal adhesions were noted in the vicinity of the anastomosis. The common bile duct was ligated in the five pigs with a patent anastomosis and the animals monitored by serum liver enzyme assays for a further 4 weeks. The pigs were then killed and laparotomy carried out. All pigs remained clinically well with no significant change in serum liver enzyme levels. At laparotomy all five anastomoses were found to be patent with a mean diameter of 95 (range 70–110) mm.

We advocate the technique of laparoscopic cholecystojejunostomy for bilioenteric drainage in advanced cancer of the head of the pancreas This method has now been used in humans.

Activated polymorphonuclear neutrophils: role as mediators of interleukin 2 induced capillary leak syndrome

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Interleukin 2 (IL-2)-based therapies provide the best response rates and prolongation of survival in patients with advanced malignant melanoma and renal cell cancer Response rates are related to the total IL-2 dose administered but the principal dose-limiting toxicity is a capillary leak syndrome which predominantly afflicts the lung Severe sepsis is also associated with a similar acute lung injury, which is mediated at least in part by activated neutrophils. Tumour necrosis factor (TNF) is a potent activator of neutrophils and may be released during IL-2 infusion Evidence was sought for neutrophil activation in ten patients with advanced malignant melanoma or renal cell cancer who developed capillary leak syndrome during a 5-day therapeutic infusion of IL-2. Plasma TNF-α levels were measured before (baseline) and on days 1 and 5 of infusion Simultaneously the expression of the neutrophil activation marker CD11b and neutrophil production of hydrogen peroxide were measured by flow cytometry and are expressed as the mean(s.e.m.) of the mean channel fluorescence (MCF) for each parameter.

	Plasma TNF-α (pg ml^{-1})	H_2O_2 production (MCF)	CD11b expression (MCF)
Baseline	7 8(1 3)	103·2(4 5)	75·4(9·8)
Day 1	153 9(10·1)*	111·9(3 7)*	121 1(18 9)*
Day 5	28 3(9·6)	111 1(4 4)*	197 6(34 1)*

* $P < 0\ 05$ *versus* baseline (Student's paired *t* test)

Plasma TNF-α levels are raised within 24 h of beginning IL-2 infusion; this is accompanied by phenotypic and functional neutrophil activation This is strong evidence of a role for activated neutrophils in IL-2-induced capillary leak syndrome and suggests means for modifying IL-2 toxicity without necessarily diminishing its therapeutic efficacy.

Effect of interleukin 2 treatment on human natural cytotoxicity

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Recombinant interleukin 2 (rIL-2) has been shown to have an antitumour effect against selected malignancies in humans. The exact nature of this antitumour effect remains to be fully elucidated but one possible mechanism of action is stimulation of natural cytotoxicity – natural killer (NK) and lymphokine-activated killer (LAK) cells This study investigated the effect of rIL-2 on blood lymphocytes of patients before and after therapy It also investigated the effect of further incubation of these lymphocytes *in vitro* with additional rIL-2.

Twelve patients with metastatic colorectal cancer were treated with rIL-2 (18 × 10^6 units m^{-2} per 24 h) for a total of 120 h Peripheral blood lymphocytes were obtained from these patients before rIL-2 treatment and at the end of the 120-h infusion Cytotoxicity of NK and LAK cells was determined using standard chromium release assays, and lymphocyte phenotypes were determined using the appropriate CD (56 etc.) monoclonal antibody and an EPICS C cell analyser Lymphocytes isolated from patients at the end of the 120-h infusion of rIL-2 were then incubated with rIL-2 (1500 units ml^{-1}) *in vitro* for 3 days and NK and LAK cytotoxicities determined

	Before rIL-2	After rIL-2	After rIL-2/rIL-2 *in vitro*
NK activity (lytic units)*	671	1392‡	1150‡
LAK activity (lytic units)*	<10	126‡	407§
CD56$^+$ (%)†	12 1(6 9)	39·2(6 9)	

Values are *mean, †mean(s.d). ‡$P < 0\ 05$, §$P < 0\ 01$ *versus* before rIL-2

These results demonstrate that there is an enhancement, *in vivo*, of natural cytotoxicity with rIL-2 therapy Maximal stimulation of NK cell activity was obtained, but only suboptimal enhancement of LAK cell activity was seen, as further incubation with rIL-2 *in vitro* produced significant augmentation of LAK cell killing Suppressor mechanisms in patients with a large tumour load may be responsible for this selective augmentation of natural cytotoxicity.

Stimulation of human tumour cell growth by recombinant interleukin 2

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Recombinant interleukin 2 (rIL-2) has recently been used to treat cancer Initial studies reported responses in up to 30 per cent of patients with selected tumours; subsequent studies have failed to confirm these response rates. The stimulation of lymphocytes by rIL-2 is well recognized, but its effect on tumour cells has not previously been investigated. This study evaluated the effect of rIL-2 on human tumour growth, using the A549 cell line (derived from a human lung cancer).

A549 cells were incubated in RPMI 1640 (10 per cent fetal calf serum) for 48 h *in vitro*, supplemented with varying concentrations of rIL-2 (expressed as units per ml culture medium). control cultures without rIL-2; 10 units ml^{-1}, 50 units ml^{-1}; 100 units ml^{-1}; 250 units ml^{-1}, 500 units ml^{-1} After 48 h incubation, rates of cellular protein synthesis were measured by incorporation of [^{3}H]phenylalanine into protein, and DNA synthesis by incorporation of [^{3}H]thymidine

	DNA synthesis (d p.m.)	Protein synthesis (d p m per mg protein × 10^2)
Control	9 335(365)	3112(307)
10 units ml^{-1}	12 669(271)*	4570(477)*
50 units ml^{-1}	12 889(255)*	4991(217)*
100 units ml^{-1}	19 448(1427)†	4528(666)*
250 units ml^{-1}	20 189(1004)†	4940(377)*
500 units ml^{-1}	22 486(1334)†	5295(713)*

Values are mean(s e m) (six cultures) d.p m , Disintegrations per minute detected in a β-counter; *$P < 0{\cdot}05$, †$P < 0\ 001$

These results provide the first documented evidence for stimulation of protein and DNA synthesis, indices of tumour metabolic activity and growth, by rIL-2 in a human cancer cell line *in vitro*. Furthermore, the presence of the P75 component of the IL-2 receptor was demonstrated in these cells, and IL-2 was detected in the nucleus, by immunohistochemistry

Monocytes from patients with obstructive jaundice show increased tumour necrosis factor and interleukin 6 production

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Monocytes have been shown to be activated to produce cytokines in sepsis and trauma and this is related to the patients' clinical outcome. Tumour necrosis factor (TNF), interleukin 1 and interleukin 6 (IL-1, IL-6) and transforming growth factor beta (TGF-β) production by monocytes from patients with obstructive jaundice were studied

Patients with obstructive jaundice ($n = 21$; 13 malignant and eight benign) without evidence of sepsis were compared with age- and sex-matched controls. Peripheral blood monocytes were purified and stimulated with lipopolysaccharide. IL-1, IL-6 and and TNF levels in the supernatant were measured by radioimmunoassay, and TGF-β by CCL60 (mink lung cell line) bioassay.

	IL-1 (fmol)	IL-6 (fmol)	TNF (fmol)	TGF-β (units ml^{-1})
Controls	14·2(3·5) (6·8–21 5)	35 6(5·0) (25 1–46 0)	2 4(0 5) (1 2–3 5)	32 3(3 6) (24 6–39 9)
Jaundiced	17·6(3·8) (9·9–25 3)	54 8(7 6)* (39 0–70 7)	32·6(8·3)* (15 5–49 6)	32·4(3 2) (25·8–39·1)

Values are mean(s e.m) (95 per cent confidence interval) *$P < 0\ 05$ (Student's *t* test)

Jaundiced monocytes showed increased IL-6 and TNF production after lipopolysaccharide stimulation but IL-1 and TGF-β levels were unchanged The increased production is higher in malignant jaundice: TNF 9·2 and 44·6 fmol; IL-6 42·7 and 50·0 fmol in patients with benign and malignant conditions, respectively Three patients who died shortly after testing had the highest TNF levels (108·2 fmol), very raised IL-6 levels (80·2 fmol) but routine IL-1 (40·0 fmol) and TGF-β (32·9 units ml^{-1}) levels

These data show that monocytes in obstructive jaundice are activated and show a higher capacity to produce the cytokines TNF and IL-6. The overproduction of these cytokines is especially high in patients with malignant jaundice and is also related to poor outcome.

Thromboxane mediates pulmonary oedema but not permeability after interleukin 2

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Immunotherapy with interleukin 2 (IL-2) is dose-limited by pulmonary oedema. Thromboxane A_2 (TxA_2) induces oedema in various settings Since IL-2 infusion also leads to raised plasma thromboxane (Tx) levels the role of TxA_2 was investigated in pulmonary and heart injury after IL-2 infusion.

Anaesthetized rats were treated with saline ($n = 13$), OKY046, a Tx synthase inhibitor (2 mg kg^{-1} h^{-1}, $n = 8$) or SQ29 548, a Tx receptor antagonist (2 mg kg^{-1} bolus, 0·2 mg kg^{-1} min^{-1}, $n = 10$) 30 min before a 1-h infusion of 1 × 10^6 units recombinant IL-2 or saline ($n = 12$) After 6 h, the wet:dry weight ratios of the lungs and heart were estimated, bronchoalveolar lavage was performed and plasma Tx was measured

	Wet.dry weight ratio		Lavage protein (μg ml^{-1})	Plasma Tx (pg ml^{-1})
	Lung	Heart		
Sham	4·05(0·09)	3·71(0·06)	460(190)	481(93)
IL-2 (saline)	4·78(0·12)*	4·09(0·11)*	1970(210)*	1290(245)*
IL-2 (OKY)	4·00(0·21)†	3·76(0·09)†	1760(265)*	102(9)†
IL-2 (SQ)	4·36(0·08)†	3·69(0·08)†	1570(316)*	998(150)*

Values are mean(s.e.m.) *$P < 0·05$ *versus* sham; †$P < 0·05$ *versus* IL-2 (saline)

IL-2 infusion led to oedema of the lungs and heart, protein leakage and elevated plasma Tx levels. The Tx synthase inhibitor and TxA_2 receptor antagonist reduced the oedema in both organs but did not prevent alveolar protein leakage As expected, plasma Tx was reduced by OKY046 but not by SQ29 548

These data suggest that TxA_2 mediates pulmonary and heart oedema but not pulmonary permeability after infusion of IL-2 in rats.

In vivo evidence for specific antityrosine kinase activity of somatostatin in the inhibition of growth of pancreatic cancers

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Somatostatin and its analogues inhibit the growth of pancreatic cancers. *In vitro* data suggest that this may be through a tyrosine phosphatase receptor which dephosphorylates the products of the growth stimulatory receptors of the tyrosine kinase receptor family· epidermal growth factor (EGF), insulin-like growth factor (IGF) 1 and 2, etc. The purpose of these studies was to investigate the interaction of the somatostatin analogue RC-160 with EGF, IGF-1 and the cholecystokinin analogue caerulein which stimulates cells through calcium and guanosine cyclic 3′,5′-monophosphate (cGMP). In the first experiment 36 Syrian golden hamsters were inoculated in each cheek pouch with H2T hamster pancreatic cancer cells and randomized to six equal groups to receive. saline, RC-160, 100 μg, EGF, 10 μg, caerulein, 10 μg, EGF plus RC-160, caerulein plus RC-160, each by intraperitoneal injection three times a day for 7 weeks. Tumour area was measured weekly. In the second experiment 24 hamsters were inoculated with H2T and randomized to four equal groups (saline; RC-160, 100 μg, IGF-1, 10 μg; IGF-1 plus RC-160) and were treated in the same way as the first experiment, but for only 4 weeks From the third week of both experiments trends emerged which persisted until the animals were killed.

	Tumour area at death (mm^2)	
	Experiment 1	Experiment 2
Saline	99(6)	37(2)
RC-160	83(7)*	25(2)*
EGF	145(12)*	—
Caerulein	102(7)	—
EGF plus RC-160	85(7)*	—
Caerulein plus RC-160	110(12)	—
IGF-1	—	48(2)*
IGF-1 plus RC-160	—	21(2)*

Values are mean(s.d.). *$P < 0·05$ *versus* control (saline) (two-way ANOVA)

This is the first *in vivo* demonstration of a trophic effect of IGF-1 on pancreatic cancer. These data support tyrosine kinase antagonism by somatostatin, but a reversal of somatostatin inhibition by cGMP stimulation, which may explain the somatostatin insensitivity of some pancreatic cancers.

Antineoplastic effects of granulocyte macrophage-colony stimulating factor

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Granulocyte macrophage-colony stimulating factor (GM-CSF) is a cytokine with established myelopoietic and potential antineoplastic effects This study examined the effects of GM-CSF on host antitumour responses in a mouse model

In study 1 mice ($n = 40$) received Lewis lung sarcoma implants (10^6 tumour cells, subcutaneously), were randomized to receive GM-CSF (1 μg day^{-1}) or saline (control) for 10 days and studied for tumour volume.

In study 2 peritoneal macrophages were harvested from mice ($n = 30$) and studied (with or without GM-CSF co-culture· 50 ng ml^{-1} per 10^6 cells) for macrophage antitumour mechanisms including oxygen free radical (O_2^-) production, nitric oxide (NO) release and non-opsonized phagocytic function (percentage macrophage ingestion of *Candida*).

	Study 1		Study 2	
	Tumour volume (ml)	O_2^- (nmol)	NO (μmol)	Percentage macrophage ingestion
Control	3·5(0·7)	0·2(0)	10(2)	8(1)
GM-CSF	1·4(0·4)*	0·7(0)†	29(1)†	27(2)‡

Values are mean(s.e.m.). *$P = 0·02$; †$P < 0·01$, ‡$P < 0·001$ *versus* controls

GM-CSF significantly up-regulated all macrophage antitumour mechanisms studied ($P < 0·01$–$0·001$). *In vivo* administration of GM-CSF significantly decreased tumour growth after 10 days. This cytokine functions through the enhancement of macrophage tumoricidal activity. These novel findings indicate the therapeutic potential of GM-CSF in the tumour-bearing host

Glycoprotein-processing inhibitors potentiate antitumour immune responses

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Swainsonine (SW) inhibits mannosidase II during *N*-linked glycoprotein processing and has recently been found to inhibit metastasis in several murine tumour models and to augment the expression of receptors for the lymphokine interleukin 2 (IL-2) on lymphocytes. This study asked whether SW might achieve these antimetastatic effects by potentiating antitumour immune responses. The effect of SW on the generation of lymphokine-activated killer (LAK) cells was examined by performing SW dose–response curves on the generation of LAK cells from human peripheral blood mononuclear (PMN) cells in response to a fixed concentration of IL-2 (1000 units ml^{-1}) *in vitro* for 3 days. Data ($n = 6$) are expressed as mean area under curve units at each concentration of SW.

	SW (μg ml^{-1})				
	0	1·0	2·0	5·0	10·0
LAK	138	159(9·6)	166(10)*	166(15·4)	151(9·1)

Values are mean(s.e.m.). $P < 0.05$ (ANOVA), $^*P < 0.05$ *versus* control (Student's *t* test)

The effects of SW on the susceptibility of tumour cells to killing by human LAK cells were also studied. COLO320 colorectal cancer cells were cultured for 3 days with varying concentrations of SW before use as target cells in the LAK cell assay which used unmodified PMN cells activated for 3 days with 1000 units ml^{-1} IL-2 alone as the effector cells. The results for these experiments (mean of three experiments) were:

	SW (μg ml^{-1}) to modify COLO320				
	0	1·0	2·0	5·0	10·0
LAK	75	93(6·9)	100(5)*	94(1·5)*	90(3·3)

Values are mean(s.e.m.) $^*P < 0.05$ *versus* control (Student's paired *t* test)

SW significantly augments human LAK cell activity and tumour cell susceptibility to LAK cells at a concentration of 2 μg ml^{-1}. SW is non-toxic and may be an important reagent for increasing the response rates of patients with malignant disease to IL-2 therapy.

Cell proliferation studies to define patients at increased risk of colorectal cancer

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The mucosa of patients susceptible to colorectal cancer appears normal but exhibits altered proliferative activity. Autoradiography, after [^{3}H]thymidine uptake, has been widely used to characterize these changes; indeed, it has been proposed as a potential biomarker. The development of a monoclonal antibody to 5-bromo-2′-deoxyuridine (BrdU) allows a more rapid and accurate identification of DNA-synthesizing (S phase) cells.

Using an *in vitro* method, BrdU labelling was analysed in a series of patients with chronic, quiescent, ulcerative colitis (UC; $n = 10$), adenomatous polyps ($n = 15$), established colorectal cancer ($n = 20$) and in normal controls ($n = 18$). Incorporated BrdU was visualized immunohistochemically. The mucosal proliferative pattern in normal subjects was compared with altered states in patients at risk of malignant change.

	Crypt label index (%)	Mean position of label cell	Label frequency in upper 40 per cent of crypt
Controls	7·8(2·3)	24·5(4·9)	2·6(3·8)
UC	11·0(3·0)	33·0(2·7)	9·2(4·7)*
Polyps	11·9(3·6)	32·4(5·9)	8·8(9·7)†
Cancer	11·3(3·6)	29·7(4·3)	4·3(4·3)‡

Values are mean(s.d.). $^*P < 0.01$; $^\dagger P < 0.05$, $^\ddagger P$ not significant *versus* controls (Wilcoxon two-sample test)

Results confirm the presence of altered proliferative activity, as measured by BrdU incorporation, in the mucosa of patients prone to colorectal cancer. Increased cell proliferation and an expansion of the proliferative compartment are common features. The upwards shift of labelled cells, expressed by the label frequency in the upper 40 per cent of the crypt, provides a useful discriminatory marker of colorectal cancer risk.

Individuals with a family history of colorectal cancer demonstrate abnormal colonic mucosal proliferation

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Individuals from kindreds with familial adenomatous polyposis and family cancer syndrome have abnormally high colonic mucosal proliferation when measured by [^{3}H]thymidine autoradiography. However, no association has been recorded when individuals are stratified into risk groups based only on a family history of colorectal cancer.

Rectal biopsies were obtained from 35 subjects with a family history of colorectal cancer, median age 41 (range 19–68) years and 21 subjects with no such family history, median age 57 (range 39–71) years. All showed normal colonoscopy. Individuals were stratified according to lifetime risk of colorectal cancer, based on their family history alone, into high risk (>10 per cent), intermediate risk (<10 per cent) and population risk (2 per cent) for controls.

Crypt cell production rate (CCPR) was used as an index of colonic mucosal proliferation, measured by the *in vitro* metaphase arrest technique.

CCPR was significantly elevated ($t = 2.12$, $P = 0.04$; Student's *t* test) in the high-risk family group ($n = 22$, mean(s.d.) 14(6·7) cells per crypt per hour) compared with controls ($n = 21$, mean(s.d.) 10(4·4)). There was no significant difference in CCPR between controls and those at intermediate lifetime risk.

Individuals at high risk of colorectal cancer because of a strong family history demonstrate abnormal mucosal proliferation.

Ileorectal anastomoses should be converted into pouches in middle-aged patients with familial adenomatous polyposis

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Prophylactic surgery for patients with familial adenomatous polyposis (FAP) should have a low morbidity rate, a good functional result and significantly reduce the chance of death from cancer. Currently the decision rests between total colectomy and ileorectal anastomosis (IRA), which gives a low morbidity rate and good function but a definite cancer risk, and restorative proctocolectomy which has a higher morbidity rate, reasonable functional result and no colorectal cancer risk.

A total of 224 patients who had undergone IRA for FAP since 1948 was studied. The chance of developing rectal cancer was 10 per cent by the age of 50 years (95 per cent confidence interval 4·5–15·5 per cent) rising steeply and significantly to 29 per cent by the age of 60 years (95 per cent confidence interval 18–40 per cent) (life-table analysis). Age at operation has no influence on the chance of developing rectal cancer, life-table analysis on two groups (under 25 years at IRA and 25 years or over) showed no significant difference ($P = 0.4$, log rank test).

Age at rectal cancer (years)	All patients	<25 Years at IRA	⩾25 Years at IRA
40	5	2	7
50	10	10	11
60	29	29	30

Values for risks are percentages

Colectomy and IRA carries a low risk of rectal cancer until after the age of 50 years, when there is a steep rise in incidence. Of patients with rectal cancer, 74 per cent had undergone sigmoidoscopy within the previous 6 months. Although most of the cancers were small, 40 per cent of patients already had lymph node or distant metastases. We conclude that the high risk of cancer despite regular surveillance means that IRAs should be converted to pouches before the age of 50 years.

Oral calcium inhibits rectal epithelial proliferation in familial adenomatous polyposis

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Dietary calcium inhibits colorectal carcinogenesis and crypt cell production rate (CCPR) in rats and might therefore diminish human rectal epithelial proliferation in patients with familial adenomatous polyposis (FAP). A double-blind trial compared the effect of dietary supplementation with oral calcium or placebo in 28 patients with FAP who had previously undergone total colectomy and ileorectal anastomosis and were attending regularly for follow-up. Patients were randomized to receive 1·5 g calcium carbonate or placebo for 6 months They were examined by sigmoidoscopy at each visit, rectal polyps were counted and the serum calcium level was measured. In 17 patients, paired rectal biopsies were taken from macroscopically normal rectal mucosa. These were divided into explants and set up in organ culture. After 15 h, vincristine (0 6 μg ml^{-1}) was added to induce metaphase arrest and samples were removed 1, 2 and 3 h later. CCPR was determined by linear regression analysis of the accumulation of arrested metaphases.

The trial was completed by 25 patients, mean age 38 (range 16–25) years The overall mean(s.e.m.) CCPR ($n = 22$) was 7·08(1·37) cells per crypt per hour but with a wide range (1·14(0·02)–30 65(2·91)). In ten patients who received placebo there was no significant reduction in CCPR (8·23(3·05)–4·80(1·26) cells per crypt per hour; $P = 0{\cdot}38$), whereas in seven patients receiving calcium CCPR was reduced by 51 per cent, from 4·72(0·48) to 2·42(0·48) ($P < 0\ 05$). Serum calcium levels were unaffected by dietary supplements Thus, oral calcium reduces rectal epithelial proliferation in FAP. As accelerated mucosal proliferation predisposes to malignancy, increased dietary calcium may protect against cancer in the long-term treatment of patients with this disease

Adverse influence on healing of high-risk colonic anastomoses by fibrin sealant

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The effect of a fibrin sealant on sutured colonic anastomoses was studied using a high-risk colonic anastomosis model. Wistar rats ($n = 104$) were randomized to have a sutured colonic anastomosis treated with sealant or left untreated, and assessed clinically until they were killed on the fourth day after operation, when contrast radiography, detailed post-mortem examination, anastomotic bursting pressure and assessment of adhesion formation were performed. The clinical outcome was worse in the glued group (systemic sepsis 18 *versus* 7 untreated, $P = 0\ 035$), which also showed a higher leakage rate (17 *versus* two, $P < 0{\cdot}001$). The median anastomotic bursting pressure was significantly higher in the glued group (96 *versus* 68 $\mathrm{cmH_2O}$, $P = 0\ 037$), which also showed excessive perianastomotic adhesion formation

Microscopic examination showed an intense inflammatory reaction around the glued anastomoses, but not in those of the untreated group.

These results indicate that sealing of sutured anastomoses with fibrin glue containing an antiproteinase impairs healing of anastomotic wounds, probably by resisting the ingrowth of vascular granulation tissue during the early stages of repair. In a further series of experiments using the same model and assessment criteria but fibrin sealant without an antiproteinase there was no significant difference between treated and untreated groups.

Cellular proliferation at experimental sutured and sutureless colonic anastomoses

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Accelerated cellular proliferation may explain the phenomenon of enhanced carcinogenesis at experimental colonic anastomoses. As tumour yield is influenced by anastomotic technique, the effect of a sutureless closure as well as different types of sutured closure on crypt cell production rate (CCPR) at the suture line was explored.

Eighty male F344 rats were used. A 5-mm transverse colotomy was created which was repaired with four interrupted 5/0 sutures of silk, stainless steel or polyglactin 910, or a sutureless closure Five animals in each group were killed after 1 week, 4 weeks, 3 months and 6 months. CCPR was assessed by the stathmokinetic technique. At each time interval the number of metaphase figures in 20 crypts was counted and plotted against time. The CCPR was derived from the slope of the regression line

In the sutured animals anastomotic CCPR was significantly greater than adjacent descending colon CCPR for at least 3 months after operation (*Table*). By contrast there was no significant elevation of the CCPR at the sutureless anastomosis compared with the adjacent colon at any time.

	CCPR (cells per crypt per hour)	
	Anastomosis	Descending colon
1 Week	10·3	7·8*
4 Weeks	10·6	7 9†
3 Months	8·7	7 7‡
6 Months	7·9	8·8

*$f = 9{\cdot}48$, $P < 0\ 005$, †$f = 10\ 3$, $P < 0\ 005$; ‡$f = 4\ 4$, $P < 0{\cdot}05$

Cellular proliferation is raised at sutured but not sutureless anastomoses for at least 3 months. This may explain why fewer experimentally induced tumours occur at anastomoses closed without sutures

Clonal theory for metastasis in colorectal cancer

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Invasion and metastasis require the release of cells from the restrictive effects of the extracellular matrix. In order to achieve this, it has been suggested that a subpopulation of cells exists within a primary tumour, providing metastatic potential and therefore rendering the tumour biologically more aggressive. In this study, it was hypothesized that a metastatic subpopulation or clone of cells could be selected *in vivo* from a primary colorectal carcinoma cell line. The *in vivo* development of metastatic variants from SW 1116 cells, originally isolated from a Dukes' A lesion, was performed in an ectopic lung model followed by further selection to establish an orthotopic liver metastasis model. The selected variant (498 Li) was then compared with the parental cell line for differences in the ability to form spontaneous metastases in the liver and lung metastasis model, invasiveness and motility *in vitro* in the Boyden chamber chemoinvasion assay, and tissue plasminogen activator (tPA) activity and collagenase type IV activity measured from cell lysates in radioimmunoassays.

Cell line	Invasiveness (cells per high power field)	Motility (cells per high power field)	Collagenase type IV activity (μg ml^{-1})	tPA activity (units ml^{-1})
SW 1116	5 8(0·6)	20·4(5·4)	0 06	5·8(0 2)
498 Li	38 9(2·3)*	67·6(6 0)*	0 5*	98·0(6 2)*

Values are mean(s.e m.) *$P < 0{\cdot}001$ (Student's t test)

This study provides evidence for the existence of a metastatic subpopulation or clone in primary colorectal cancer cells. Understanding in detail the different steps involved in metastasis will facilitate the development of specific strategies to prevent the progression of this disease process to the metastatic stage.

Mechanical bowel preparation before colorectal surgery: results of a prospective randomized trial

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Mechanical bowel preparation (MBP) before elective colorectal surgery has become established surgical practice. Recently this practice has been challenged[1]. The aim of this trial was to determine the need for

MBP before elective colorectal surgery in a prospective randomized trial

Patients undergoing elective colorectal surgery were randomized to receive either oral polyethylene glycol lavage solution or no MBP. All patients received standard perioperative intravenous antibiotics and intraoperative saline lavage. After surgery, patients were examined for wound infection (discharge of pus), intra-abdominal sepsis and anastomotic leakage

In all, 179 patients have been studied, 86 receiving MBP. The principal pathology was carcinoma (92 per cent), and 31 per cent of patients underwent anterior resection There was no difference in the wound infection rate, five of 86 with MBP *versus* seven of 93 without MBP ($P = 0\cdot77$). The rate of intra-abdominal sepsis was significantly higher in those patients receiving MBP (eight of 86 compared with two of 93 without MBP; $P = 0\cdot05$), as was the rate of anastomotic leakage (eight of the 67 in whom bowel continuity was restored *versus* one of 67 without MBP; $P = 0\cdot03$).

These results suggest that MBP using polyethylene glycol lavage does not reduce the septic complication rate of colorectal surgery and may be detrimental.

1 Irving AD, Scrimgeour D. Mechanical bowel preparation for colonic resection and anastomosis. *Br J Surg* 1987; **74**: 580–1

Biochemical and molecular markers for predisposition to abdominal aortic aneurysm in the Irish population

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Clinical, biochemical and genetic parameters in patients with abdominal aortic aneurysm (AAA) and their families which may have predictive value are being examined Family history and ultrasonographic data were obtained, and blood drawn for biochemical and genetic analysis in 54 patients, 28 controls and 62 relatives of patients Three patients gave a positive family history of AAA and three siblings with AAA were identified No aneurysms were detected in the control group Several biochemical markers have been evaluated. Results were.

	n	Positive family history†	α_1-Antitrypsin*	Leucocyte elastase*	HDL cholesterol*
Patients	54	6 (11)	138(10)	0·51(0·07)	1·11(0·03)
Controls	28	0 (0)	142(18)	0·77(0·12)‡	1·43(0·13)‡

*Values are mean(s.d.), †values in parentheses are percentages ‡$P < 0\cdot05$

These data indicate that patients with AAA do not have any major protease or antiprotease imbalance, have significantly lower leucocyte elastase activity and have lower high-density lipoprotein (HDL) cholesterol levels than control subjects. Two polymorphic 'microsatellite' marker loci in the region of the haptoglobin locus have been investigated. Considerable variation has been observed between the normal American and Irish populations in the frequencies of certain alleles at both loci, indicative of considerable genetic variation between these populations A new allele has been found at each locus which is present in the Irish but not in the American population One of these new alleles seems to appear only in the Irish patient and patient-relative groups and not in the Irish control group This may indicate a previously undiscovered chromosome 16 gene–disease association for AAA in the Irish population

Familial aortic aneurysm: guidelines for screening

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Patients with peripheral arterial disease and siblings of patients with abdominal aortic aneurysm (AAA) appear to be at increased risk of having an asymptomatic AAA, screening detecting aneurysms in 10–13 per cent and 12–28 per cent of cases respectively. The purpose of this study was to investigate how sibling screening could become more effective.

In all, 28 families (25 brothers and 28 sisters) have been screened for AAA by ultrasonography, and information collected about smoking, medical history and serum cholesterol Aortas were categorized as aneurysmal, wide or normal (maximum external infrarenal anteroposterior diameters >3 cm, 2·5–2·9 cm and <2·5 cm respectively).

Among screened siblings five brothers and one sister (all over 60 years old) had an AAA of diameter >3·0 cm; three more brothers (over 60 years old) had a wide aorta and five brothers and three sisters (under 60 years of age) had a wide aorta A wide or aneurysmal aorta was more common among brothers (13 of 25) than among sisters (four of 28) ($P = 0\cdot017$, χ^2 test). A wide or aneurysmal aorta was also associated with a history of smoking more than ten packs per year (15 of 17) compared with those with a normal aorta (19 of 36) ($P = 0\cdot035$, χ^2 test) The presence of a wide or aneurysmal aorta was not associated with hypertension or increased serum cholesterol Among the siblings of probands under 60 years old at the time of AAA resection a wide or aneurysmal aorta was found in nine of 16 compared with eight of 37 siblings of probands over 60 years old ($P = 0\cdot014$, χ^2 test)

These results indicate that the efficiency of screening siblings of patients with AAA could be improved by limiting screening to brothers with a smoking history and/or siblings of younger patients The familial component appears to be greatest in the younger patients.

Pulse-generated run-off and colour duplex ultrasonography in assessing the lower limb arteries for angioplasty

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Patients with symptoms of claudication which may be amenable to angioplasty currently need to undergo arteriography The suitability of a lesion for dilatation depends on its morphology and the distal run-off Non-invasive assessment of the lower limb vasculature may avoid unnecessary arteriography

Colour duplex ultrasonographic scanning of femoral and popliteal arteries was performed to establish whether the vessels were normal, stenosed or occluded. The pulse-generated run-off (PGR) system was used to assess the distal vasculature, in particular the number of distal calf vessels in continuity with the popliteal artery. In 65 lower limbs duplex scanning gave the following results compared with angiography

	Sensitivity	Specificity	Accuracy
Occlusion (*n* = 28)	96	98	97
Stenosis (*n* = 17)	94	98	97
Atheromatous vessel (*n* = 16)	100	100	100
Disease-free (*n* = 4)	100	100	100

Values are percentages

PGR and arteriographic evaluation of run-off agreed in 54 limbs, however in 11 (17 per cent) PGR demonstrated run-off better than did arteriography, a not unusual finding in the presence of ischaemia All 23 limbs suitable for angioplasty were correctly identified and satisfactorily dilated

A combination of duplex scanning and PGR offers a non-invasive alternative to arteriography for assessing patients, and may thereby restrict arteriography to those patients with a lesion suitable for angioplasty

Preoperative prediction of calf vessel patency for femorodistal bypass

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The ability of pulse-generated run-off (PGR), pedal arch assessment, ankle:brachial pressure index (ABPI) and conventional preoperative arteriography to predict successfully the vessel for distal anastomosis was studied in 25 patients undergoing femorodistal bypass for critical ischaemia Investigations were graded on a scale of 0–2 for each calf vessel, with the exception of PGR combined with pedal arch assessment which was graded 0–3 The score for each vessel was expressed as a fraction of the maximum possible score.

The correlations between combined scores for all three calf vessels were compared. PGR with arch assessment correlated significantly with PGR alone ($r_s = 0{\cdot}57$, $P < 0{\cdot}005$), with ABPI ($r_s = 0{\cdot}51$, $P < 0{\cdot}005$) and with preoperative arteriography ($r_s = 0{\cdot}35$, $P < 0{\cdot}05$).

Mean scores for vessels grafted were 0·50 for PGR with arch assessment, 0·48 for PGR alone, 0·42 for ABPI and 0·12 for preoperative arteriography.

The scores for grafted vessels were compared with those for non-grafted vessels. Significant differences were found only for PGR with arch assessment ($P < 0{\cdot}05$), and for PGR alone ($P < 0{\cdot}01$) (Mann–Whitney U test). The sensitivity and specificity of PGR were 0·88 and 0·3; ABPI 0·72 and 0·28; intraoperative arteriography 0·84 and 0·7; and preoperative arteriography 0·4 and 0·22 for grafted and non-grafted vessels respectively.

These findings suggest that PGR and arch assessment is the preoperative investigation of choice before femorodistal bypass grafting.

Low molecular weight heparin in the prevention of recurrent venous thromboembolism

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Long-term therapy using warfarin sodium, although effective in preventing recurrent venous thromboembolism, is associated with a significant morbidity rate. The present study was undertaken to find out whether low molecular weight heparin (LMWH) could be used as an alternative to warfarin therapy.

One hundred consecutive patients suffering from acute deep vein thrombosis (DVT) were randomly allocated to receive, over a 3-month period, either a fixed self-administered daily dose of 5000 units LMWH or warfarin – the dose of warfarin being adjusted to maintain a prothrombin index of twice the control value. Patients were reviewed at 4-week intervals to assess compliance with the treatment, monitor side-effects and document evidence of recurrence Repeat phlebography was performed at the end of the study period (or earlier if symptoms developed) to document evidence of recurrence. Cost-effectiveness of each treatment was estimated by economic analysis, taking into account the number of visits required to attend hospital for monitoring of the treatment and the need for hospitalization because of complications of therapy

The results were analysed according to intention to treat. Five patients developed recurrent DVT; three in the group on LMWH and two in the group receiving warfarin. None of the 50 patients receiving heparin had any side-effects to the treatment. Five patients in the warfarin group developed haemorrhagic and allergic complications; three of these required hospitalization for further treatment Cost analysis of the two methods of treatment indicated that there could be savings of approximately £500 per patient when LMWH is used.

Both warfarin therapy (adjusted dose) and therapy using a fixed daily dose of LMWH are equally effective in preventing recurrence of DVT. However, warfarin therapy, in spite of strict laboratory control, is associated with more frequent side-effects and appears to be more expensive.

Low molecular weight heparin inhibition of intimal hyperplasia in vein grafts

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Intimal hyperplasia caused by smooth muscle cell proliferation is a well recognized cause of vascular graft failure. Several studies have demonstrated that the mitogenic activity of platelet-derived growth factor can be modified by heparin and its low molecular weight derivatives This study addressed whether these agents are useful in the prevention of intimal hyperplasia *in vivo*

The effect of subcutaneous low molecular weight heparin (LMWH) therapy on intimal hyperplasia following arterial bypass grafting was examined. An animal model using the carotid artery of the rabbit was used. (This work was approved by the appropriate Home Office department.) New Zealand White rabbits ($n = 24$) underwent interposition vein grafting of the carotid artery. Animals were randomly assigned to control or treated groups. Treated animals received 60 anti-Xa units kg^{-1} subcutaneous LMWH daily for 1 month. Animals were then killed, graft patency was assessed and the vessels harvested for analysis of intimal hyperplasia. Intimal hyperplasia in carotid arteries and vein grafts was measured using a computerized image analysis system. A statistically significant reduction in the degree of intimal hyperplasia seen in the arterial component of the distal anastomoses of carotid vein grafts was achieved using subcutaneous LMWH (control median (interquartile range) 0·44 (0·37–0·55); LMWH 0·27 (0–0·37); $P < 0{\cdot}05$, Mann–Whitney U test). There was no difference in the degree of intimal hyperplasia seen in the vein grafts themselves (control 0·21 (0–0·54); LMWH 0·23 (0–0·72)). Grafts in the LMWH group had an improved patency rate (70 per cent) compared with those in controls (57 per cent).

This study has shown that subcutaneous LMWH effectively inhibits the development of intimal hyperplasia after vascular grafting. This effect, together with the antithrombotic properties of LMWH, may help to prolong vascular graft patency.

Venous reflux control by external compression

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Compression stockings and bandages may act by reducing venous reflux The aim of this study was to establish the mechanism of action of external compression on venous function Both lower limbs of 36 patients (median age 59 (interquartile range (i q r.) 45–65) years) were assessed by duplex ultrasonography. There were 17 limbs with popliteal vein reflux, 19 with long saphenous vein reflux, 21 with short saphenous vein reflux and 15 normal limbs. A water-filled external compression cuff was applied around the knee. The cuff was then inflated gradually, while continuously assessing the vein for reflux using ultrasonographic imaging through the cuff. The cuff pressure was noted when reflux was abolished or the vein completely occluded.

	Popliteal vein ($n = 17$)	Long saphenous vein ($n = 19$)	Short saphenous vein ($n = 21$)
Reflux abolished			
Number of veins	4	8	3
Pressure (mmHg)	62 (60–64)*	31 (22–83)†	58 (50–85)‡
Reflux not abolished			
Number of veins	13	11	18
Occlusion pressure (mmHg)	89 (67–96)*	87 (70–108)†	75 (65–93)‡

Values for pressures are median (i q.r.) *$P < 0{\cdot}05$, †$P < 0{\cdot}01$, ‡P not significant (Wilcoxon rank sum test for unpaired samples)

In a small proportion of veins, valvular competence was restored by external compression. In the majority, complete occlusion of the vessel was required to abolish venous reflux The high pressures required to achieve these effects exceed those exerted by compression therapy It is concluded, therefore, that correction of valvular incompetence is unlikely to be the mechanism of action of stockings and bandages in venous disease.

Calf venous pump function following ankle fracture

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Trauma to calf veins after lower limb fracture impairs venous outflow and delays return of normal limb function. Calf venous muscle pump function may also be relevant. Calf venous function was assessed in 26 patients with ankle fractures – where direct venous injury is minimal Air plethysmography (APG) and duplex scanning were performed following internal fixation and before application of a below-knee plaster cast (week 0), after immobilization and removal of the cast at 6 weeks, and following mobilization at 12 and 18 weeks after injury. APG was used to measure calf venous volume (VV), rate of venous filling (VFI), ejection volume fraction (EVF) and residual volume fraction (RVF) in both fractured and contralateral (control) limbs. Duplex scans showed no evidence of femoral or popliteal vein obstruction at any examination There was no difference in VFI in control or fractured limbs at any assessment and VV was increased only in the fractured limb at week 0. Other APG measurements in fractured (F) and control (C) limbs were:

	Week 0	Week 6	Week 12	Week 18
EVF (C)	55·9(19·5)	55·6(21·9)	60·3(14·9)	57·5(17·5)
EVF (F)	18·1(12·1)*	28·5(21·2)*	39·0(16·0)*	57·7(16·3)
RVF (C)	42·1(22·2)	48·5(23·7)	38·8(13·1)	33·0(16·5)
RVF (F)	87·0(14·3)*	82·2(16·8)*	64·7(18·8)*	39·9(16·2)

Values are mean(s.d.) percentages $^*P < 0{\cdot}001$ *versus* control (Student's t test)

These data demonstrate that after internal fixation of ankle fractures and subsequent immobilization for 6 weeks there is significant reduction in calf venous pump function, which does not recover until 18 weeks after the original injury. This prolonged reduction in calf venous pump function may contribute to the delayed return of normal limb function following ankle fracture

Comparison of saphenofemoral ligation with and without long saphenous vein stripping

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Stripping of the long saphenous vein (LSV) may prevent recurrence of varices, but this has not been demonstrated using objective criteria. The aim of this study was to determine whether the addition of LSV stripping to saphenofemoral junction (SFJ) ligation would prevent residual reflux shown by vascular laboratory investigation.

Forty-two patients with primary LSV reflux confirmed by duplex ultrasonography and photoplethysmography (PPG) gave consent for inclusion in the study In all, 62 limbs were treated by SFJ ligation and avulsion of varices Patients were randomized to undergo stripping of the LSV in the thigh or no additional treatment Three months after surgery patients were reinvestigated using duplex ultrasonographic imaging and PPG tests of venous reflux to establish the extent of persisting varices

	Before surgery		After surgery		
	SFJ and LSV reflux	Thigh perforators	Residual LSV reflux	Residual perforators	Median increase in PPG time (%)
LSV stripping ($n = 32$)	32	8	9*	2	52
No stripping ($n = 30$)	30	8	19*	6	47

$^*\chi^2 = 6{\cdot}4$, $P < 0{\cdot}05$

LSV stripping resulted in far fewer persisting incompetent LSVs in the thigh than SFJ ligation alone PPG refilling times were improved to approximately the same extent in both groups No limb in either group developed paraesthesia in the distribution of the long saphenous nerve These data suggest that LSV reflux is more completely abolished by combining LSV stripping with SFJ ligation

Role of rectal contraction during defaecation

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During normal defaecation the intrarectal pressure is observed to rise In the absence of a reference catheter in the pelvis, the contribution of abdominal straining and rectal contraction to this intrarectal pressure rise is unclear. The aim of this study was to examine the mechanism of intrarectal pressure elevation using the empty bladder to measure intrapelvic pressure.

Ten consecutive female patients with no gastrointestinal symptoms undergoing urodynamics were studied A double-lumen catheter was placed in the rectum to measure pressures during the filling and evacuation of a water-filled rectal balloon Intrapelvic pressure was recorded using a second intravesical catheter.

Before rectal filling, abdominal straining (Valsalva's manoeuvre) produced identical rises in intrarectal and intravesical pressure.

The mean(s.d.) instilled volume required for a call to stool was 96(28) ml During filling the mean(s d) rectal pressure increased from 2(0·5) to 18(4) $\mathrm{cmH_2O}$. The intravesical (pelvic) pressure remained unchanged at 2(1) $\mathrm{cmH_2O}$. Evacuation of the rectal balloon produced an increase in intrarectal pressure from 18(4) $\mathrm{cmH_2O}$ (end filling pressure) to 68(15) $\mathrm{cmH_2O}$ The intravesical pressure increased from 2(1) to 51(18) $\mathrm{cmH_2O}$ The true intrarectal pressure (intrarectal minus intrapelvic) did not rise during defaecation

These data suggest that the rise in intrarectal pressure during rectal evacuation can be explained by increased intrapelvic pressure alone These observations suggest that rectal contraction is not important in defaecation and also support the hypothesis that posterior pelvic floor contraction is important for normal defaecation

Importance of the thickness of the normal anal sphincters: an ultrasonographic study

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Anal sphincter thickness was measured ultrasonographically using a 1-cm tip diameter endoprobe in 30 asymptomatic subjects (13 men, age range 20–51 years, 17 women, age range 20–75 years). Of the subjects 23 were young (20–23 years) and seven were older (41–75 years) Scans were video recorded and measurements of sphincter thickness made from film hard copies The internal anal sphincter (IAS) was measured at its thickest portion in the lower anal canal, its borders lying between the submucosa and the external anal sphincter (EAS) The EAS was measured at the lowest point in the anal canal, its borders being the submucosa and the coccyx

The EAS was significantly thicker in men than in women ($P < 0{\cdot}02$). The IAS showed no significant difference in respect of sex ($P > 0{\cdot}05$) The EAS was significantly thinner with age ($P < 0{\cdot}005$) This is in agreement with the diminution of striated muscle bulk in the ageing process. The IAS appeared significantly thicker with age ($P < 0{\cdot}0002$), which could be explained by degenerative or infiltrative change in its internal structure

Throughout the group the EAS thickness correlated inversely with the IAS thickness ($P < 0{\cdot}001$), increased thickness of one seems to compensate for any reduction in the other. Appropriate sphincter manometry showed correlation between the anal canal resting pressure and the sum of the thicknesses of the two sphincters ($P < 0{\cdot}001$) Thus, although the visualized thicknesses of the two sphincters vary, they do so proportionally and their sum reflects their tonic activity, important in the control of continence

Comparison of the properties of the internal anal sphincter and the conjoint longitudinal coat of the anal canal

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The internal anal sphincter (IAS) and the conjoint longitudinal coat (CLC) form two discrete layers of smooth muscle within the anal canal The latter is the continuation of the longitudinal muscle of the rectum and has an unknown function The purpose of this study was to compare the properties of the two muscle layers.

Small strips of muscle from both layers (18 strips from three abdominoperineal resection specimens for each response) were mounted for isometric tension recording in a perfused organ bath at 36°C Tone was initially established by loading the strips with the equivalent of a 1 g weight This spontaneously increased in IAS (187(4·3) per cent of original tone) but decreased in CLC strips (21·7(7·1) per cent of original tone, $P < 0{\cdot}01$, Student's unpaired t test). In this state carbachol, a cholinergic agonist, caused dose-dependent relaxation of IAS strips (5×10^{-6}–10^{-4} M) but contraction of CLC strips (5×10^{-7}–10^{-4} M) Hexamethonium (10^{-6} M), a ganglion-blocking agent, had no effect on these responses but they were abolished by atropine (10^{-6} M), a cholinergic (muscarinic) receptor antagonist Noradrenaline caused dose-dependent contraction of both tissues (5×10^{-6}–10^{-4} M), a response which was abolished by phentolamine (10^{-6} M), an α-adrenergic receptor antagonist.

These results indicate that the behaviour of the two smooth muscle layers of the anal canal is different and suggests that defaecation may involve CLC contraction

Prolonged internal sphincter relaxation/inhibition: an underestimated problem in incontinence

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To assess the contribution of episodes of prolonged sphincter relaxation in the pathogenesis of faecal incontinence, ambulatory anal sphincter electromyography and manometry were carried out on 56 patients with neurogenic faecal incontinence (36 women; median age 51·5 (range 32–97) years) and 23 continent controls (13 women; median age 47 (range 29–80) years)

The median relaxation rate per hour was 4 (range 2–7) for controls and 9 (range 7–12) for patients ($P < 0\,03$). Upper anal canal pressure (UAC) decreased by a median of 20 (range 10–35) cmH$_2$O in the control group, but mid-anal canal pressure (MAC) did not change. Both UAC (median 25 (range 15–30) cmH$_2$O; $P > 0\,05$) and MAC (median 25 (range 14–26) cmH$_2$O; $P < 0\,001$) fell in the incontinent group, of whom only 16 exhibited external sphincter recruitment. Rectal pressures increased (median 11 (range 2–20) cmH$_2$O) above UAC in 55 per cent of the control group but never exceeded MAC. In the incontinent patients, rectal pressures also increased (median 21 (range 7–35) cmH$_2$O; $P < 0\,01$) but exceeded MAC in 65 per cent of cases, accounting for episodes of incontinence. Moreover, whereas internal sphincter relaxation never exceeded 10 s in controls, 35 per cent of incontinent subjects exhibited episodes of prolonged relaxation: median 28 (range 25–34) s; $P < 0\,001$

We conclude that these episodes contribute to the pathogenesis of incontinence, and would be missed using conventional laboratory methods.

Lateral ligament division during rectopexy causes constipation but prevents recurrence of prolapse

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Although rectopexy has a reputation for causing constipation the mechanisms by which it does so are not known Denervation of the rectum by division of the lateral ligaments may be important. The 1-year results of a prospective study are presented in which patients with full-thickness rectal prolapse were randomized to undergo either rectopexy with division (group 1 ($n = 14$), 12 women, mean age 50 years) or preservation (group 2 ($n = 12$), 11 women; mean age 57 years) of the lateral ligaments.

Patients were studied before and 1 year after rectopexy. Study included assessment of the frequency of defaecation, the time spent straining, need for laxatives and suppositories and use of digitation to enable evacuation, measurement of anal pressures, anorectal sensation and pudendal nerve latencies.

Continence significantly improved in both groups of patients. In group 1 the number of patients with constipation increased (three before surgery, ten after, $P < 0\,01$). Mean resting anal pressure and voluntary contraction pressure were higher after rectopexy in all patients. Rectal electrical sensory threshold increased significantly in group 1 (27 6 mA before *versus* 56 7 mA after surgery, $P < 0\,01$) but not in group 2 (39 *versus* 34·9 mA, $P > 0·05$). However, there was no correlation between deterioration of the electrical rectal sensation and development of constipation In group 2 there was recurrent full-thickness rectal prolapse in four patients and mucosal prolapse in two, there was no recurrence in group 1.

This study has demonstrated that division of the lateral ligaments during rectopexy results in a higher incidence of constipation and a significant change in rectal electrical sensation However, preservation of the lateral ligaments is associated with an increased recurrence rate of rectal prolapse

Pudendal nerve function after restorative proctocolectomy using the eversion technique

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The aim of this study was to determine whether the technique of anorectal eversion – useful in the 'difficult pelvis' – results in impaired pudendal nerve function.

Nineteen patients underwent restorative proctocolectomy with end-to-end ileoanal anastomosis, without mucosal stripping, by the eversion technique Before operation they underwent laboratory tests of anorectal function, and after operation these were repeated at a median of 10 (range 4–18) months, together with assessment of pudendal nerve latency, using the St Mark's pudendal nerve electrode. A control group of ten patients of similar age and sex distribution was also studied.

	Anorectal eversion	Controls
Pudendal nerve latency (ms)	2 6 (2·3–3·8)	2 4 (1 7–2·6)
Supramaximal stimulus (mA)	22·6 (11·6–31 4)	14 0 (10·5–20·5)

Values are median (interquartile range) *P* not significant

We conclude that the technique of anorectal eversion as used in the course of restorative proctocolectomy does not impair the function of the pudendal nerves.

Manometric studies and clinical results after coloanal and ileoanal anastomosis

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The aim of this study was to establish whether coordinated activity exists between the anal sphincter and the neorectum above the anastomosis A total of 29 patients was studied, 12 after rectal excision and coloanal anastomosis for carcinoma and 17 after restorative proctocolectomy with quadruplicated ileal reservoir and ileoanal anastomosis. Each patient was interviewed and underwent tests of anorectal function a median of 1 year after operation.

	Coloanal ($n = 12$)	Ileoanal ($n = 17$)
Bowel frequency (day^{-1})	4·5 (2–12)	5 (2–8)*
Urgency (n)	5	0*
Faecal leakage (n)	8	1*
Maximum resting anal pressure (cmH$_2$O)	56 (11–160)	69 (40–107)
Maximum tolerated volume (ml)	55 (28–208)	275 (170–760)*
Maximum anal pressure during sampling reflex (cmH$_2$O)	30 (0–55)	58 (50–124)*
Volume for maximal sphincter inhibition (ml)	50 (20–60)	240 (100–420)*

Values are median (range). *$P < 0\,01$

We conclude that functional outcome is related to anal sphincter proprioception. The anal sphincteric 'sampling' reflex and the functional capacity of the neorectum in combination seem to be the governing factors.

Pouch patients are less likely to suffer from excess bile acid loss

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Bile acid absorption is determined by the absorptive capacity of mucosa, and the time spent in the intestine. Because the ileum is important for reabsorption of bile acids a miniature flux chamber has been used to measure quantitatively ileal mucosal uptake and transport of taurocholic acid after restorative proctocolectomy and in control groups.

	Uptake	Transport
Pouch ($n = 20$)	12 7(4 7)	1 03(0·6)
Ulcerative colitis ($n = 19$)	13·0(4·8)	1·3(0 8)
Constipation ($n = 11$)	14·5(5·5)	0·8(0 8)
Cancer ($n = 7$)	13·1(4·2)	0·98(0 8)

Values are mean(s.d.) expressed in μg per g wet weight per 45 min

Parameters of gastric, small bowel, pouch and whole gut transit were measured using a ^{99m}Tc-diethylenetriamine penta-acetate-labelled solid meal followed with a γ camera in 14 pouch patients and ten ileostomy controls

The mean(s.d.) whole gut residence time (time in contact with mucosa) in 'meal hours' was longer in pouch patients (11·8(2·6)) than in ileostomy patients (6·6(2·2)) ($P < 0{\cdot}002$, Mann–Whitney U test). Because the gastric residence (pouch 1·64(0·4), ileostomy 1·3(0·5)) and small bowel residence (pouch 4·3(1·9), ileostomy 5·3(2·0)) are similar, the increased whole gut residence is caused by time spent in the pouch (5·9(1·5) meal hours).

Restorative proctocolectomy does not adversely affect ileal mucosal absorption of bile acids *per se*. Thus, the increased residence time in pouch patients may mean that they are less likely to suffer excess bile acid loss.

Histological changes in the gracilis neosphincter muscle following long-term electrical stimulation

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An electrically stimulated gracilis neoanal sphincter has been developed for patients with faecal incontinence and as part of a reconstruction following sphincter excision. Long-term electrical stimulation (LTES) is employed in an attempt to transform the predominantly type 2, fatiguable gracilis into a type 1, fatigue-resistant muscle.

This study aimed to determine whether the gracilis muscle fibre type and fibre size were changed by transposition and LTES

Superficial biopsies from the mid-portion of the gracilis muscle of six patients, before and 7–12 weeks after LTES (2–15 Hz), were snap-frozen in isopentane–liquid nitrogen Cryostat sections were stained with myosin adenosine 5′-triphosphatase to permit differentiation of type 1 and 2 fibres The number of type 1 and 2 fibres in each biopsy and the diameter of each fibre were measured (at least 200 fibres per biopsy were typed and measured)

	Before LTES	After LTES	P*
Percentage of type 1 fibres	33·7(4·7)	72·3(19·6)	<0·01
Type 1 fibre diameter (μm)	41·0(12·0)	28·7(6·5)	<0·05
Type 2 fibre diameter (μm)	37·8(7·8)	29·8(11·5)	<0·05

Values are mean(s.d.). *Student's paired t test

These results demonstrate a significant increase in the number of type 1 fibres following transposition and LTES and a significant decrease in the size of both type 1 and 2 fibres

This study confirms that LTES of the gracilis neosphincter muscle results in conversion to a predominantly type 1 muscle, more appropriate to sphincteric function

Protective effects of traumatic immunosuppression

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The macrophage plays a pivotal role in the immunosuppressive response to trauma, but the role of post-traumatic macrophages in host response to subsequent infection is unclear. This study examined host response to intra-abdominal sepsis following injury Pair-fed Swiss mice ($n = 200$) were randomized to control or hind limb amputation and studied in two groups

Group 1 mice ($n = 105$) on days 1 and 3 after surgery were given endotoxin (lipopolysaccharide (LPS), 60 mg kg^{-1}) or underwent caecal ligation and puncture (CLP) and studied for mortality (LPS, percentage survival, CLP, median survival in hours).

Group 2 mice ($n = 95$) were killed on days 1 and 3, and peritoneal macrophages were studied for trauma-induced oxygen free radical priming responses (O_2^- with or without LPS co-culture, nmol), tumour necrosis factor (TNF, pg ml^{-1}) and interleukin 6 (IL-6, pg ml^{-1}) release and cell surface-LPS receptor binding (percentage)

Differences between baseline and LPS-induced oxygen free radical release (O_2^-) were blunted on day 1 following amputation ($\Delta O_2^- = 0{\cdot}15$) compared with controls ($\Delta O_2^- = 0{\cdot}45$, $P = 0{\cdot}001$) Proinflammatory cytokine (TNF, IL-6) responses and LPS receptor binding were also significantly decreased on day 1. These findings correlated with significantly increased survival following sepsis (LPS, CLP) at this time

	Group 1		Group 2		
	TNF	IL-6	LPS receptor	LPS	CLP
Control					
Day 1	467(163)	2528(227)	34(14)	8	24
Day 3			28(0·1)	0	24
Amputation					
Day 1	154(40)*	1220(480)	12(2)†	75‡	72§
Day 3			31(4)	10	24

Values are mean(s.d.) (three to five experiments) *$P = 0{\cdot}001$, †$P = 0{\cdot}02$; ‡$P < 0{\cdot}001$; §$P < 0{\cdot}05$ *versus* control

Post-traumatic early immunosuppression appears protective, the mechanism may be blockade or internalization of the LPS receptor following injury

L-Arginine-dependent pathway mediates traumatic immunosuppression

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Lymphocyte dysfunction occurs following trauma but the mechanisms are unclear Macrophage-derived prostaglandin E_2 and L-arginine metabolites have been implicated as inhibiting lymphocyte function This study examined potential immunosuppressive L-arginine-dependent (oxidative, nitric oxide (NO) and non-oxidative, arginase) pathways activated by trauma. Mice ($n = 160$) were randomized to control or hind limb amputation groups. Twenty-four hours after injury, peritoneal macrophages and splenocytes were harvested and studied (with and without the NO inhibitor N-monomethyl-L-arginine (NMMA) and the arginase inhibitor L-lysine) as follows· allogeneic mixed lymphocyte culture (MLC), NO and arginase synthesis.

	Control	Amputation
MLC (c.p.m.)	12(1)	5(1)*
Plus NMMA	21(2)†	8(0·4)
Plus L-lysine	9(3)	12(1)†
NO (μmol)	31·2(5)	19·8(4)*
Arginase (nmol)	9(1)	21(2)*

Values are mean(s.e.m.) *$P < 0{\cdot}05$ *versus* control, †$P < 0{\cdot}05$ *versus* same group control

Amputation inhibited lymphocyte function L-Lysine, but not NMMA, up-regulated lymphocyte function in the amputation group, correlating with decreased NO levels but increased arginase production by amputation group macrophages. NMMA, but not L-lysine, enhanced lymphocyte function in the control group only, correlating with higher production of NO in these animals This demonstrates that L-arginine-dependent metabolites are important in lymphoregulation. NO appears to be the predominant suppressor mechanism in the normal state, while trauma induces arginase activity that may be suppressive through depletion of extracellular arginine required for normal lymphocyte function

Interleukin 6 primes neutrophils for sustained respiratory burst *in vitro*

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In humans with sepsis, interleukin 6 (IL-6), which possesses diverse biological activity, is correlated with mortality rates A sustained surge of IL-6 in porcine acute lung injury, maximal at 180 min, has been found. The neutrophils polymorphonucleocytes (PMNs) may play a critical role in vascular endothelial damage characteristic of this form of acute lung injury, through generation of superoxide (O_2^-) anions. It was hypothesized that IL-6 mediates vascular injury by priming the PMN respiratory burst PMNs were isolated from healthy human volunteers by dextran sedimentation and density gradient centrifugation, to 95 per cent purity and 98 per cent viability. PMNs were incubated with increasing concentrations of recombinant human IL-6 for 180 min O_2^- generation was measured using a kinetic assay based on superoxide dismutase-inhibitable reduction of ferrocytochrome *c*. Low doses of IL-6 (0·01, 0·1 and 1 ng ml^{-1}) showed no up-regulation of O_2^- production (data not shown) However, PMNs incubated with 1000 ng ml^{-1} IL-6 showed marked sustained up-regulation of O_2^- production (*Table*). Results are expressed as nanomoles O_2^- per 10^6 PMNs per minute over a 10-min period.

IL-6 (ng ml^{-1})	Time (min)					
	0	2	4	6	8	10
0	0	0·49	1·04	1·21	1·09	0·85
10	0	0·89	1·24	1·21	1·15	0·91
10^2	0	0·96	1·69	1·92	1·71	1·55
10^3	0	1·17*	2·97*	3·87*	4·57*	4·32*

*$P < 0·05$ *versus* control (ANOVA)

This sustained increase in respiratory burst is in contrast to the acute, shorter-lived increase noted with tumour necrosis factor and interleukin 1 by other workers. We conclude that IL-6 primes PMNs for an enhanced respiratory burst over a prolonged period and may therefore be critical in continuing a septic response initiated by other cytokines.

γ-Linolenic acid inhibits respiratory burst and tumour necrosis factor priming of neutrophils

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Essential fatty acids and their metabolites are important in immune function This study investigated the effects of the *n*-6 fatty acid, γ-linolenic acid (GLA), on the tumour necrosis factor (TNF) priming and respiratory burst of neutrophils Purified neutrophils (10^7 ml^{-1}) from normal volunteers were co-cultured with GLA with or without TNF for 10 min and then stimulated by f-Met-Leu-Phe (FMLP, 1 µM). The luminol-dependent chemiluminescence was recorded and expressed as mean(s.e.m.) counts per second. The effect of GLA on the cytosolic free Ca^{2+} concentration in neutrophils was measured using ratio fluorometry of FURA-2

	Control	GLA 1·0 µM	GLA 10·0 µM	GLA 50·0 µM
Without TNF	9697(2134)	10766(2080)	9889(1566)	1417(636)*
With TNF	12079(2475)†	9366(2959)	7726(1329)*	1962(514)*

*$P < 0·05$ *versus* control, †$P < 0·05$ *versus* control without TNF (Student's paired *t* test)

To determine whether this inhibition was the result of cytotoxicity, the cytosolic free Ca^{2+} and trypan blue exclusion were measured. Neither measurement gave evidence for cytotoxicity of GLA up to 100 µM. Furthermore there was no inhibition of the FMLP-induced transient rise in cytosolic free Ca^{2+}.

These data show that GLA inhibits neutrophil respiratory burst and neutrophil priming by TNF. This suggests that GLA may be of benefit to patients with excessive inflammatory oxidation, for example in obstructive jaundice and severe sepsis.

Neutrophil priming by interleukin 8 in normal and obstructive jaundice patients

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It has been reported that the cytokine interleukin 8 (IL-8) has major effects on neutrophils, and may be involved in inflammatory reactions. The effects of IL-8 on neutrophil respiratory burst from normal and jaundiced patients have therefore been studied.

Ten patients with obstructive jaundice and a matched control group without sepsis were studied. Neutrophils from peripheral blood were purified and maintained in Krebs medium. Cells (5×10^7) were precultured with or without IL-8 (1·0 ng ml^{-1}) for 10 min and the luminol-dependent chemiluminescence recorded after adding f-Met-Leu-Phe (FMLP, 1·0 µM) together with cytochalasin B (5·0 µg ml^{-1}) The results were expressed as mean(s.e.m.) counts per second

	Without IL-8	With IL-8	*P**
Control group			
Before FMLP	94·1(22·3)	163·3(57·0)	0·30
After FMLP	6434·0(1176·0)	9873·0(2089·0)	0·02
Jaundiced group			
Before FMLP	127·8(44·4)	103·7(21·9)	0·09
After FMLP	15324·0(3018·0)	11473·0(1904·0)	0·03

*Student's *t* test

The neutrophil respiratory burst induced by FMLP was significantly greater in jaundiced patients than in controls ($P < 0·05$, Student's *t* test) In contrast there was no 'priming' induced by IL-8 in the neutrophils from jaundiced patients whereas in controls they were enhanced up to twofold.

These data show that healthy neutrophils are primed by IL-8 whereas jaundiced neutrophils are activated but fail to be further primed by IL-8 The clinical relevance of this phenomenon remains to be elucidated.

Role of hypotension in the increased gut permeability in ischaemia–reperfusion

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Reperfusion of ischaemic limbs after bilateral hind limb ischaemia leads to an alteration in intestinal permeability and systemic endotoxaemia The role of prolonged hypotension which follows lower limb reperfusion was investigated in 30 male Wistar rats.

Treatment by 3 h ischaemia and 2 h reperfusion was compared with two controls – 5 h anaesthesia without ischaemia, and ischaemia alone. The effect of hypotension after 3 h ischaemia without releasing tourniquets was assessed by an infusion of 28 µg min^{-1} kg^{-1} sodium nitroprusside and controlled withdrawal of arterial blood to a mean arterial pressure (MAP) of 75 mmHg for 2 h. Intestinal permeability was measured by injecting horseradish peroxidase (HRP) into the isolated ileocaecal loop 15 min before killing the animals. Transmucosal passage of HRP beyond intercellular tight junctions was assessed on electron microscopy by an independent pathologist. Systemic endotoxin was measured by a chromogenic *Limulus* amoebocyte lysate assay before tourniquet application, tourniquet release and after lower limb reperfusion.

On reperfusion after 3 h ischaemia MAP fell from a mean(s.d.) of 107(5) mmHg to 76·0(4·3) mmHg ($P < 0·05$, ANOVA) compared with 75(1·2) mmHg and 74(1·5) mmHg after normovolaemic and haemorrhagic hypotension. One of six animals demonstrated HRP permeability after general anaesthesia, ischaemia alone and after hypovolaemic or normovolaemic hypotension In contrast, all six animals following 2 h reperfusion showed permeability to HRP ($P < 0·05$, Fisher's exact test). Endotoxin increased from 21·8(2) pg ml^{-1} initially to 30·7(2·6) pg ml^{-1} after 2 h reperfusion ($P < 0·05$, ANOVA) but did not increase in any other group.

Reperfusion damage is not a consequence of hypovolaemic or normovolaemic hypotension but may be caused by release of systemic mediators from reperfused ischaemic tissue leading to gut mucosal damage

Multilumen central venous lines used for the administration of total parenteral nutrition: an audit

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A prospective audit of 1135 percutaneous central venous lines placed between November 1988 and November 1989 for 563 patients monitored by a nutritional support team was performed to assess the complications of multilumen central venous lines used for the administration of total parenteral nutrition (TPN).

TPN was administered via 879 triple-lumen lines, 219 pulmonary artery catheters, 31 double-lumen lines and six single-lumen lines. The overall complication rate was 11·5 per cent. Infective complications accounted for 4·7 per cent (catheter-related sepsis (CRS) 4·4 per cent; site infection 0·35 per cent), complications at insertion 1·5 per cent (pneumothorax 0·7 per cent); and late non-infective complications 6·9 per cent (dislodgement 4 per cent). Kaplan–Meier life-table analysis showed an increase in the overall complication rate but not the rate of CRS with duration of catheterization.

TPN was administered via a single line for 326 patients, two to 14 lines were required for 227 patients. Analysis of 427 lines changed by replacement at a new site as compared with 159 catheters changed over a guidewire showed a total complication rate of 11 per cent for lines placed at a new site compared with 15 per cent for lines changed over a guidewire (*P* not significant). The rate of CRS was 0·5 per cent for lines placed at a new site compared with zero for lines changed over a guidewire. There were no differences in the survival of the new lines by life-table and log rank analysis when comparing these two groups.

We conclude that multilumen central venous lines may be used safely for the administration of TPN. No evidence was found to support routine periodic change of central venous lines used for TPN administration. Change of central venous lines for all except infective complications should be performed over a guidewire.

Glutamine peptide supplementation stimulates muscle protein synthesis in surgical patients receiving glutamine-free amino acids

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Muscle glutamine levels fall and nitrogen excretion increases after surgery. Glutamine dipeptide provision prevents this fall and also decreases nitrogen excretion. This study investigated a possible mechanism by studying the effects on muscle protein synthesis of alanylglutamine (Ala–Gln) supplementation of standard non-glutamine-containing amino acid solution in patients undergoing major surgery. Studies were approved by the local ethical committee. Eight patients (age range 66–79 years) had undergone oesophagectomy for carcinoma. They received parenteral nutrition including a conventional amino acid solution and were studied on the third day after operation when a constant infusion of the tracer [^{13}C]L-leucine was given. Muscle protein incorporation of [^{13}C]L-leucine was measured over two 4-h periods. In the first, the conventional solution was supplemented with alanine plus glycine as a control mixture isonitrogenous with the Ala–Gln given in the second period. Tibialis anterior muscle biopsies were taken at 4 h and 8 h; muscle obtained at surgery provided basal tissue. The ^{13}C enrichment of blood, intramuscular free leucine (IM-Leu), α-ketoisocaproic acid (KIC) and muscle-protein leucine were analysed by mass spectrometry. Tracer labelling of IM-Leu and plasma KIC were used as indices for the true leucyl-transfer RNA labelling in calculating muscle protein synthesis. Muscle protein synthetic rates (mean(s.d.)), without *versus* with Ala–Gln, were 0·025(0·004) *versus* 0·043(0·004) per cent per hour (KIC) and 0·039(0·003) *versus* 0·078(0·008) per cent per hour (IM-Leu). These results indicate a marked anabolic effect of glutamine dipeptide supplementation in patients after surgery.

Octreotide protects against endotoxin-induced impairment of renal function

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Previous studies have shown that octreotide ameliorates hepatic necrosis and renal tubular damage following *Escherichia coli* endotoxin administration in rats. The aim of the present study was to establish whether the beneficial effects of octreotide on the liver and kidney could be explained by alterations in blood flow to these two organs.

Groups of male Wistar rats ($n = 10$) received either intraperitoneal endotoxin (2 mg 100 g^{-1}) or saline. A further group received octreotide immediately before and 12 h after administration of endotoxin. Hepatic and renal blood flow were measured by the microsphere method and renal function was assessed by plasma clearance of Mag3, a tubular function agent.

Octreotide prevented the hepatic necrosis and renal tubular damage observed in rats treated with endotoxin alone. Cardiac output was significantly reduced in the two groups that received endotoxin ($P < 0·001$, ANOVA). There was no significant difference in hepatic or renal blood flow between the groups. Mag3 clearance was significantly reduced in the group that received endotoxin (mean(s.e.m.) 0·76(0·05) ml min^{-1} 100 g^{-1}) compared with controls (1·11(0·09) ml min^{-1} 100 g^{-1}). However, in the octreotide group there was no impairment of renal function (1·23(0·09) ml min^{-1} 100 g^{-1}).

Endotoxaemic renal tubular damage appears to result from a direct effect on renal tubules rather than alterations in kidney haemodynamics. Renal tubular function is protected by prior administration of octreotide, although its precise mode of action is unclear.

Correspondence

Severe haemorrhagic complication following needle or open biopsy of a breast mass: suspect angiosarcoma

Sir

Angiosarcoma is considered to be an exceedingly rare form of breast malignancy, which occurs in younger women and is associated with a poor prognosis[1,2]. We wish to draw attention to an unusual feature of this tumour, namely a severe local bleeding tendency following biopsy.

A 43-year-old woman presented with a rapidly growing mass in the right breast. Clinically the tumour was assessed as a $T_1N_0M_0$ carcinoma. She was sent for fine needle aspiration (FNA) biopsy which was interpreted as suspected malignant cells. Following the procedure the patient developed a large haematoma, measuring 5 × 6 cm, which obscured the original mass. During 2 weeks of local treatment the haematoma did not reduce in size. Definitive treatment of the suspected carcinoma (in the form of lumpectomy with frozen section and axillary dissection) was therefore delayed. Instead, it was decided to perform an open incisional biopsy and evacuate the haematoma. During the procedure there was diffuse bleeding from the biopsy site and haemostasis was extremely difficult to achieve. A suction drain removed almost 500 ml during the first day after operation A full coagulation profile was examined and appeared normal. The biopsy specimen revealed a diagnosis of a grade I–II angiosarcoma of the breast. Simple uneventful mastectomy was performed 1 week later and the patient referred for chemotherapy

During 10 years of clinical experience in a busy teaching hospital we have not previously encountered the formation of a large haematoma following FNA of a breast mass, nor have we seen severe bleeding after an incisional breast biopsy. Thus, we believe that haemorrhagic complications constitute a specific feature of this vascular tumour. To the best of our knowledge, this aspect has not been previously described in the relevant literature[1–4].

We conclude that the unexpected development of haematoma or haemorrhage after needle or open breast biopsy should alert the clinician to the possible diagnosis of angiosarcoma of the breast.

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Use of a resorbable mesh graft to obtain haemostasis from the cut surface of the liver after hepatic resection

Sir

We are writing with regard to the article by Prêtre *et al* on resorbable mesh grafts used to obtain haemostasis after liver resection (*Br J Surg* 1991, **78**· 361–2) This alluded to the major role of suture and electrocautery to obtain haemostasis on the cut surface of the liver. The use of a resorbable Vicryl (Ethicon) mesh as a tamponade has been previously described and a clinical need for such material is apparent[1]. The authors used microcrystalline collagen powder between the mesh and the raw surface to obtain haemostasis. This utilizes the known effects of collagen on the intrinsic clotting mechanisms and platelet adherence. It is likely that the collagen, rather than the mesh alone, was responsible for haemostasis. Recently we reported the use of a composite collagen–Vicryl mesh for the repair of the cut surface of the kidney in three patients who had undergone partial nephrectomy[2] This new material, constructed from Vicryl mesh with layered collagen film on each surface, achieved haemostasis and prevented urinary leakage Previous *in vivo* studies[3] had shown the composite mesh to elicit little inflammatory response and to be resorbed in 90 days. This mesh is currently available for clinical use only in France. It offers advantages over Vicryl mesh alone in that it has inherent haemostatic properties, requiring no additional collagen powder, and is more likely to restrict biliary leakage than a porous Vicryl mesh alone.

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Pancreatic tissue and ductal pressures in chronic pancreatitis

Sir

We read with interest the recent paper by Jalleh et al. (*Br J Surg* 1991; **78**. 1235–7). This study confirmed previous work in humans and in animal models. While we accept that there are different ways of measuring tissue pressure, we believe that the method employed by the authors is not truly representative of tissue pressure. The values measured appear to be too high and, in theory, at these pressures all parenchymal blood flow would cease. The values quoted must represent resistance of the tissues to a saline infusion rather than tissue pressure.

We have studied pancreatic tissue pressure using a direct puncture needle technique with a low pressure transducer. We showed that in normal cats basal pancreatic tissue pressure was negative and on stimulating secretion there was virtually no change in its value Cats with obstructive chronic pancreatitis had a greater basal pancreatic tissue pressure which increased further after secretory stimulation. This increase was abolished by decompression of the main pancreatic duct. These pressures suggested to us that the chronically inflamed pancreas was involved in a compartment syndrome We then measured pancreatic blood flow[1,2] and showed in chronic pancreatitis that the basal blood flow was lower than in the normal pancreas Secretory stimulation which increased blood flow in the normal pancreas caused a significant decrease in chronic pancreatitis. Decompression of the main pancreatic duct was associated with an improvement in basal blood flow, and the normal increase in blood flow on secretory stimulation was restored We consider that these results showed that the chronically inflamed pancreas was involved in a compartment syndrome. This might provide an explanation for the intractable pain of chronic pancreatitis, the efficacy of ductal decompression and the phenomenon of disease progression.

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1. Karanjia ND, Widdison AL, Leung FW, Lutrin FJ, Reber HA. Pancreatic blood flow in chronic pancreatitis· the effect of decompression of the main pancreatic duct. *Pancreas* 1990, **5**: 713
2. Karanjia ND, Widdison A, Leung F, Lutrin FJ, Chang YB, Reber HA. Blood flow alterations in chronic pancreatitis. effects of secretory stimulation. *Gastroenterology* 1990; **98**: A221.

Medical audit: use of routine erect abdominal radiographs

Sir

Several sources[1–4] including the National Radiological Protection Board[5] (NRPB) have suggested that only supine abdominal and erect chest radiographs should be obtained routinely in the assessment of acute abdominal cases and that erect abdominal radiographs should not be obtained routinely The main reason suggested is that the information obtained from the erect abdominal radiograph does not influence patient management Reduction in radiation dose to the population and radiographic costs would also result

In October 1989 such films were still obtained routinely at one hospital in our teaching centre, but not in another As a result, we set out to assess practice in several UK hospitals and to assess the value of the erect abdominal radiograph in our hospital

In October 1989 survey questionnaires were sent to 44 UK hospitals. Half were sited in university medical teaching centres (TCs), the other half being a random selection of district general hospitals (DGHs) across the country, 40 replies were received. These showed that in ten hospitals (six TCs, four DGHs) routine erect abdominal radiographs were no longer obtained, while this practice still occurred in 30 hospitals (14 TCs, 16 DGHs)

In July 1991, resurvey of the latter 30 hospitals resulted in 27 replies. At 14 of these (eight TCs, six DGHs), policy had changed in that routine erect abdominal radiographs were no longer obtained; policy was unchanged in 13 (three TCs, nine DGHs, one undesignated) At two of these 13 (both DGHs), policy was under review at the time of resurvey

There was awareness of the NRPB guidelines of 1990[5] recommending that erect abdominal radiographs should no longer be routine Discussion regarding their routine use had occurred in radiology departments of all but one hospital (this incidentally being the undesignated hospital above, the identification on the questionnaire form having been removed before its return)

A prospective study of 100 consecutive acute abdominal emergencies was carried out at our hospital, in which erect abdominal radiographs were still routine Junior surgical registrars were asked to assess patients on the basis of history, clinical examination and blood tests, but initially to assess only the erect chest and supine abdominal radiographs A questionnaire was filled in at this stage, with particular note made of the clinical management plan The erect abdominal radiograph was then assessed and the questionnaire completed, with particular note made of any change of management plan In no case did the information obtained from the erect abdominal radiograph result in a change of patient management This study gave identical results in this respect to a similar study by Field *et al.*[4]

All of the above information, along with results from previous studies on this topic, were discussed at an audit meeting in our hospital, which resulted in the local decision to comply with NRPB guidelines.

Results from our survey suggest that practice elsewhere has also changed; perhaps this is related to the publication of NRPB guidelines and the introduction of formal medical audit within the National Health Service There seems to be no significant difference between the pattern of practice in TCs and DGHs However, there now appear to be few TCs at which practice has not changed Practice at the numerous DGHs is more difficult to assess, because of the large numbers (approximately half of the DGHs surveyed have yet to change their practice) If this proportion were representative of other DGHs, then this would involve a considerable number of hospitals We believe that such hospitals should review this practice, and suggest that any clinicians who resist the change should produce evidence to support the case for continuing to obtain routine erect abdominal radiographs in the assessment of acute abdominal cases

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1 Hayward MWJ, Hayward C, Ennis WP, Roberts CJ A pilot evaluation of radiography of the acute abdomen *Clin Radiol* 1984; **35**· 289–91
2 Greene CS Indications for plain abdominal radiology in the emergency department. *Ann Emerg Med* 1986; **15**. 257–60
3. Simpson A, Sandeman D, Nixon SJ, Goulbourne IA, Grieve DC, Macintyre IMC. The value of an erect abdominal radiograph in the diagnosis of intestinal obstruction. *Clin Radiol* 1985; **36** 41–2
4 Field S, Guy PJ, Upsdell SM, Scourfield AE. The erect abdominal film in the acute abdomen: should its routine use be abandoned? *Br Med J* 1985; **290**. 1934–6
5. Documents of the NRPB patent dose reduction in radiology Vol 1, No. 3, 1990

Perioperative blood transfusion does not promote recurrence and death after mastectomy for breast cancer

Sir

We read with interest the experience of Eickhoff *et al.* on the association between blood transfusion and tumour recurrence following mastectomy for breast cancer (*Br J Surg* 1991, **78** 1358–61).

We have performed a similar retrospective review on 315 consecutive patients who underwent potentially curative resection for primary colorectal carcinoma between April 1985 and April 1989 One hundred of these patients received transfusions during the same hospital admission when the resection took place. The remaining 215 patients received no perioperative transfusion. Patient characteristics in the transfused and non-transfused groups are outlined in the *Table* below

	Transfused ($n = 100$)	Non-transfused ($n = 215$)	P
Mean(s d) age (years)	69 9(11 0)	68·8(11·3)	0 4
Sex ratio (M F)	42 58	108:107	0·2
Mean(s d) haemoglobin level (g/dl)	11·5(2·0)	13·5(1·8)	<0 001
Mean(s d) white blood cell count ($\times 10^9$/litre)	8·5(2 9)	8·3(2·7)	0·5
Mean(s.d.) operating time (min)	120 6(49 1)	108 7(39 8)	<0 001
Anastomosis (sutured stapled)	48·52	104.111	0 3
Tumour site (rectum colon)	52·48	114.101	0·3
Tumour stage (n)			
I	11	28	0 5
II	52	123	
III	37	64	

At the end of a mean follow-up of 25 months there was no difference in the incidence of tumour recurrence between transfused and non-transfused patients (23 0 *versus* 22 3 per cent respectively, $P = 0\ 3$) Cox's proportional hazards regression model was used on the data to assess the simultaneous influence of covariates Again there was no evidence of a relationship between transfusion and tumour recurrence or mortality rate The only independent and significant variables associated with the risk of recurrence were tumour stage and anastomotic technique

As discussed in the comprehensive review by Francis recently[1], neither our study nor that of Eickhoff *et al.* can answer the question of whether there is a causal relationship between transfusion and tumour growth However, both these studies serve as useful reminders that there is at present no convincing clinical evidence of an adverse effect of transfusion on human cancer.

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1. Francis DMA Relationship between blood transfusion and tumour behaviour. *Br J Surg* 1991; **78**· 1420–8.

Book reviews

Surgical Diagnosis and Management: a Guide to General Surgical Care. 2nd ed.

D. C. Dunn and N. Rawlinson 216 × 138 mm. Pp 630 + x. Illustrated. 1991. Oxford Blackwell. £17·95

This is by no means a small book: there are 630 pages of small print, weighing 1 lb on my kitchen scales. The first edition has been justly popular, its format being singularly clear and readable (Our housemen particularly like the wide margins which leave them space to annotate the text.) In its adolescence, problems and weaknesses are still apparent, although the book remains lusty and shows great promise.

It is rather too large and heavy to be carted round in all but the most determined houseperson's pocket. The senior author and his panel of 12 subeditors are mostly consultants at Addenbrooke's; the junior author completed his BChir 7 years ago, and is doing neurosurgery, and it shows! Although the prefaces to both editions and the blurb on the back target this book at senior medical students and housemen, in my view the emphasis of the text has shifted subtly away from the neophyte at the bedside to the senior house officer surgical postgraduate

For the houseman there is insufficient emphasis on what he or she can reasonably be expected to undertake and cope with unaided, and it lacks clear guidelines on when more senior help should be sought. Thus, for myself, although I would like my new houseman to take an intelligent interest in why we insert drains, what I really want him to grasp from day 1 is that he has no authority to take them out without asking the person who put them in!

For the senior house officer it has become too often a description of 'what they do at Addenbrooke's'. I think it *is* reasonable to nit-pick in a book of this type in its second edition, mainly because it sets out to be authoritative: if our houseman were to cross-match 2 units of blood and tip the end of the bed each time we did a haemorrhoidectomy, he would cause a sensation!

I am confident that there will be a third edition, and when there is I hope that another houseman author will be recruited, and that the subeditors will be more junior and drawn from a spread of institutions.

Despite all this, there is an enormous amount that is excellent here, so I *do* think that it is worth buying for senior medical students and housemen. If you are thinking of giving a copy to your favourite niece or nephew at St Elsewhere's, it might be as well to enclose a small bottle of Tipp-Ex.

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Handbook of Medicolegal Practice

J. P. W Varian. 215 × 137 mm Pp 194 + ix Illustrated. 1991. Oxford Butterworth–Heinemann. £19 50

This easily readable small handbook is edited and compiled by an orthopaedic/hand surgeon with contributions from anaesthetists, surgeons of all disciplines, and prominent members of the legal profession. In readily comprehensible terms it provides guidance and advice on the compilation of insurance and medicolegal reports, the role and conduct of the medical witness in court cases, and other aspects of medical legal practice alien to the average medical practitioner. While in no way attempting to be comprehensive, contributions from experienced practitioners in the major disciplines of medical work cover the common pitfalls and sources of litigation, and provide sound advice as to how to avoid them In an era of increasing controversy regarding informed consent and in a climate of increasing litigation, this book will find a valuable place on the shelves of trainee and experienced practitioners alike.

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Common Problems in Pediatric Surgery

J. L Grosfield. 234 × 156 mm. Pp. 310 + xv. 1991. USA· Mosby Year-Book

This book was written to provide a concise guide for general and paediatric surgical residents and other specialists involved in the care of infants and children. It is also directed at nurses and medical undergraduates. As recognized, it does not address all issues in paediatric surgery but confines itself to a discussion of the more frequently encountered surgical problems.

There are six sections in all, encompassing discussions on inguinal and umbilical hernia, acute abdominal conditions, gastro-oesophageal disorders, hepatobiliary and pancreatic disorders, paediatric trauma and head and neck lesions. It is refreshing to see a full section on paediatric trauma, but the book would have benefited from a discussion on common solid tumours Nevertheless, there is an impressive authorship list and each chapter is written by a practising paediatric surgeon whose individual preference therefore shines through A clinical case presentation introduces the chapter and serves to focus the reader's attention. Reference lists are minimal and the book would have benefited from more illustrations.

Overall this is a nicely written book which is comprehensive and well laid out I am confident that it will be useful to undergraduates and surgical residents alike. It is a welcome and worthwhile addition to the Common Problems series.

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Interventional Radiation Therapy: Techniques – Brachytherapy

R Sauer 275 × 220 mm. Pp 398 + xii. Illustrated. 1991 Germany. Springer-Verlag.

This fascinating book covers many topics of considerable interest to general and specialist surgeons. Few will be aware, for instance, of the wide applicability of radioactive implantation therapy in fields such as prostate cancer and malignant brain tumours, though many will know, through close collaboration with their radiotherapy colleagues, of the important role played by brachytherapy in head and neck tumours, and of the enormous contribution made by implant techniques in the local control of breast cancer. Many of the chapters in this volume provide a powerful argument supporting the initial use of conservative non-surgical techniques in both early and advanced primary solid cancers. Since the success of radiotherapy is closely related to dose, brachytherapy, with its ability to offer very high local dosage, coupled with a rapid fall off 3–5 cm from the tumour, can result in a near-ideal approach. I particularly enjoyed the authoritative chapter from Papillon and colleagues at Lyon, and chapters on prostatic carcinoma by the New York and Freiburg groups, the former an analysis of over 1000 patients treated at the Memorial Sloan–Kettering Hospital (with an overall median survival rate of almost 10 years). Inevitably there is some information overlap but by and large I felt the chapters grouped within each section to be reasonably complementary The more recent technique of interstitial hyperthermia, with or without external beam irradiation, is also well covered in the final section of the book, and the important area of gynaecological brachytherapy, possibly the most widely used application in cancer medicine today, is well covered by nine chapters comprising some 70 pages overall.

I doubt that this book will find a wide surgical readership, but it certainly ought to be available in general medical and surgical libraries since, like all specialists, surgeons nowadays need to develop at least a passing familiarity with the tricks that the other side might wish to bring into play. Most of the Authors are well known and respected in their field, and the Editor has managed a nice balance between European and American contributors

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Human Cross-sectional Anatomy

H Ellis, B. M. Logan and A Dixon 356 × 254 mm. Pp 180. Illustrated 1991 Oxford Butterworth–Heinemann. £29 50.

More years ago than I care to remember or admit, afternoons would be spent in the anatomy room poring over jars and Perspex or glass cubes and boxes The containers held a sizeable proportion of a former population of Newcastle upon Tyne sliced in many different directions and preserved for ever in some mysterious, rather murky fluid which contained just enough debris to act as a time-saving blizzard at examination or *viva voce* sessions. Then, and in retrospect, the slices did not help my understanding of anatomy

For the past 15 years we have become used to seeing or asking for a computed tomography (CT) scan as often as we used to ask for a chest X-ray or plain abdominal film. In this book we witness the marriage of Mr Anatomy Oblivion and the delectable, enchanting Miss C. T Scan, daughter of Mr G. N Houndsfield. The conjugal product is a transport of delight, on the left-hand page we have the anatomical slice and on the right the corresponding CT scan The plane of the scan is shown, there is a key of easily read annotations cross-referencing structures in X-ray and anatomical slice, and a set of notes gives a brief description of the slices and their contents. This marriage should last to a golden wedding. Its offspring will be a forgiving of our anatomy teachers, fond memories, a new understanding of the anatomy pot, and an improved interpretation skill in CT scans.

At about 33 pence per slice we receive 90 quality plates This is an excellent marriage and, unlike some others, cheap at the price

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Essentials of Clinical Surgery

J. H Davis, R S Foster Jr and R. L Gamelli 286 × 223 mm. Pp. 611 Illustrated. 1991. St Louis Mosby-Year Book £27.

As the range and depth of surgical knowledge becomes ever wider and more complex, it becomes increasingly difficult to find good single volume texts to recommend that contain enough detail to be useful while remaining wide enough in scope *Essentials of Clinical Surgery*, produced by three American professors from Vermont and Illinois, is aimed specifically at undergraduate students who require such a concise text This book starts with one great advantage because it is an abridged version of the much more comprehensive *Clinical Surgery* which can be used to obtain more detail. At the beginning of each chapter in this book, the parent chapter in *Clinical Surgery* is identified for easy reference In addition, useful suggestions for further reading are included at the end of each chapter for those in quest of further knowledge.

The book is divided into three sections The first and smallest part (45 pages) covers the clinical manifestations of common surgical problems. It opens with a general chapter on evaluation of the surgical patient, covering the principles rather than the practice of case history and examination and problem-orientated medical records. There are then specific chapters on the assessment of patients with abdominal pain, masses, fever, shock and alterations in levels of consciousness

The second section (167 pages) covers patient management It starts with a chapter on patient procedures, ranging from simple catheterization and venous access through to chest drains and suture technique. The succeeding chapters cover topics such as fluid and electrolyte management, coagulation and transfusion, renal failure, nutritional support and the management of sepsis The section ends with a chapter on the specific problems of paediatric surgery and organ transplantation These two sections were thought to be particularly useful by a number of junior house officers in the UK

The remainder of the book (387 pages) consists of an organized approach to surgery dealing with each organ or system in turn The overall balance between the different conditions and systems is appropriate, with common conditions receiving the necessary prominence. At the end of each chapter there is a tabular summary of the diseases of that organ or system, showing the incidence, signs and symptoms, differential diagnosis, tests, recommended treatment, and the morbidity and mortality rates for easy revision These chapters offer a concise overview but would need to be supported by an appropriate pathology textbook Although there are some differences in practice between the UK and the USA, the recommendations for investigation and treatment in this book are, in general, applicable to medical students on both sides of the Atlantic.

This is a hardbacked and sturdy book of 611 pages, with a particularly readable print. The two-column layout with generous margins makes the text more digestible, as the illustrations, although excellent, are relatively few in number. Overall, considering the price of £27, it is extremely well produced

In view of its very reasonable price and comprehensive coverage I feel that this book can be warmly recommended to medical undergraduates or any others who seek a concise textbook of surgery.

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Surgical Management. 2nd ed.

N J O'Higgins, G D. Chisholm and R C. N. Williamson, eds. 276 × 206 mm Pp. 1007 Illustrated. 1991. Oxford Butterworth–Heinemann. £49 50.

Writing a comprehensive textbook has always been difficult and is getting more and more so. The range of subject matter grows all the time, knowledge and practice change more quickly than in conventional publications, and contributors and editors are ever more busy In consequence the advice tended a quarter of a century ago is still sound, but is still disregarded for a number of reasons[1] There is apparently a demand and money to be made, there is the compelling urge of authors and editors which is almost a disease, though of course a productive one. One sign of this is that *Surgical Management* requires a second edition 8 years after its successful launch

The editors hope that the book will give guidance to those sitting higher examinations and also be a companion to the practising surgeon As to the first, assessment, in the UK at least, is undergoing change though the implications of this for the curriculum are sometimes hard to assess. The early chapters of the book on principles address effectively most of the knowledge necessary for the scientific basis of the practice of surgery and are as up to date as is possible given the problems to which I have already referred. As to the second, I am a little less confident because the confines of size have inevitably reduced the amount of detail and straightforward practical advice that can be conveyed. I could, for example, find little on the precise diagnosis and management of supramalleolar ulcer of varicose origin, this was not mentioned at all under varicose veins and referred to only in passing in the section on plastic surgery. Although human immunodeficiency virus infection is mentioned a number of times, the question of what policies to adopt with the seropositive patient and the influence of the virus on surgical disease, particularly in sub-Saharan Africa, is not considered. Closer to home, the symptoms that might be ascribed to piles are poorly discussed and though lateral sphincterotomy for fissure is mentioned the operation is not described nor is its possible effect on continence considered The problems of effective editorship are illustrated by the fact that adult respiratory distress syndrome is described twice in nearly identical terms without any cross-reference Inevitably, laparoscopy gets only minor consideration in two areas where it is now a strong performer – minimally invasive surgery and diagnosis in the acute abdomen

However, such obsolescence is what the quoted paper referred to as an unfair target for the snide reviewer. This text is a worthy one, well produced and with, for the most part, good and relevant illustrations, though I do not think that the picture of a well known and expert professor contemplating the control panel of a lithotriptor contributes a great deal to surgical education. It will certainly steer the surgical trainee in what is perceived as the right direction, though his or her knowledge will require considerable supplementary feeding from other sources

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1. Dudley HAF Textbooks: a time to stop *Lancet* 1966; **i**: 589–90.

A Color Atlas of Endovascular Surgery

R. A White and G. H. White 216 × 279 mm Pp. 200. Illustrated. 1991 Philadelphia· J B Lippincott $129·50.

'The thin fibrous cap of an atheromatous plaque had ruptured, exposing fatty gruel, extracellular lipid and abscess-like material visible on angioscopy. After dissolution of prestenotic thrombus with a clot-buster, the artery was atherectomized and a smooth intimal surface achieved' Angiogram reports like this already exist. The message of this atlas is that urgent restoration of flow in narrowed arteries is virtually within the grasp of the interventionalist. His or her repertoire will include new instruments such as an Excimer laser, ultrasonic ablator and stent. Intravascular imaging will show red and white thrombus adhering to the endothelium, yellow atheroma, and deeply fissured xanthomatous plaques before rupture

Surgeons need feel no threat from this percutaneous wizardry. Rather, there is cause for satisfaction that good outcomes for difficult clinical problems are being achieved in a brief hospital stay and at minimal discomfort and risk And which clot-buster? The choice lies between streptokinase, tissue plasminogen activator and urokinase, with no indication of the preferred agent so far

This atlas is reasonably priced, easy to read and has numerous colour pictures on most pages It is highly recommended.

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Rigid Fixation for Maxillofacial Surgery

M. R. Tucker, B C. Terry, R. P. White Jr and J E. Van Sickels 286 × 219 mm. Pp 408 + xv.. Illustrated. 1991 Philadelphia. J.B. Lippincott. $160

The first part of this very useful book deals with the historical development of rigid internal fixation, and an attempt is made to explain the basic concepts which are illustrated with clear diagrams. The effects of mandibular immobilization on masticatory apparatus are highlighted, with particular reference to the pathophysiology of immobilization Part 2 deals with the management of facial fractures using rigid internal fixation. There are several useful case studies but the quality of some of the radiographs could have been better. In view of the availability of miniplates for rigid internal fixation there are fewer indications for the use of large plates in treating facial fractures, but the Authors have felt the need for a separate chapter on the use of large plates for the purposes of clarification. Transoral open reduction of condylar fracture, as described in this book, is difficult to accomplish and almost unnecessary. The complications of rigid internal fixation are clearly described Part 3 is devoted to the use of rigid internal fixation in orthognathic surgery. Advantages and disadvantages are meticulously evaluated and a well balanced view is stated. In orthognathic surgery the surgical cuts can be planned to allow the use of miniplates effectively. There are several case studies included in the text and very useful points are illustrated with good diagrams and clinical pictures. There are no undue claims in favour of rigid internal fixation in this book.

I enjoyed reading this book and recommend it to oral and maxillofacial surgeons interested in the management of maxillofacial trauma and orthognathic surgery who wish to achieve the highest standards possible It will also be of interest to junior hospital staff and those preparing for the Fellowship exams of The Royal Colleges of Surgeons.

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Care of the Critically Ill Patient in the Tropics and Sub-tropics

D. A. K. Watters, I H. Wilson, R. J. Leaver and A. Bagshawe. 235 × 155 mm Pp. 450 + xiv. Illustrated 1991. Basingstoke Macmillan Education. £40.

The problem with most textbooks is that they are written for doctors practising in well appointed western hospitals. Those working in developing countries with limited facilities must find this disturbing and annoying This book sets out to redress the balance.

The direct and simple language should allow those with English as a second tongue to follow it easily. It covers, in a very practical manner, a large number of subjects, from surgical and medical emergencies, through trauma, to obstetric and paediatric problems. All sections are explicitly written with an emphasis on simple yet effective advice. Key points are highlighted and tables and algorithms are clearly presented. I particularly enjoyed the sections on snake bites and on malaria, so often restricted to small print, end-of-chapter comment in standard texts. The section on practical procedures tells the reader, frequently, that advanced technology equipment is often not available in developing countries owing to expense, and that ingenious alternatives are available – using a three-way tap and an aneroid sphygmomanometer to measure arterial pressure is but one Descriptions of bedside carotid angiography and burr holes remind us that computed tomography and nuclear magnetic resonance imaging are available in few developing countries.

This is not a classical text, but it is a straightforward guide to what to do when you do not have sophisticated equipment and the main centre is miles away. It is aimed at the isolated doctor or nurse who has to look after all-comers, whatever the problem It covers a lot of ground in relatively few pages, but gives suggestions for further reading. I would certainly pack it if I were travelling to the third world and would recommend it to those who have become steeped in high technology, if only to remind them of the reality outside their ivory towers. I am sure it will be found on the shelves of many rural hospitals and clinics.

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Clinical and Experimental Approaches to Dermal and Epidermal Repair: Normal and Chronic Wounds

A Barbul, M D. Caldwell. W. H. Eaglstein, T K. Hunt, D Marshall, E. Pines and G Skover, eds. 235 × 160 mm. Pp. 497 + xviii. Illustrated 1991. New York Wiley–Liss.

This book is the edited symposium proceedings from the Third International Symposium on Tissue Repair held in Florida in January 1990 This was a multidisciplinary meeting involving surgeons, physicians, dermatologists, pathologists and biologists, with representatives from industry. Regretfully the book is not international; of the 91 contributors only five were not from North America. This bias is reflected throughout, including the Editors and references. The symposium proceedings from the Second Symposium (which I also reviewed for *The British Journal of Surgery*) were based on biochemistry and basic research into growth factor technology, whereas this publication is much more clinical in its orientation

Would healing technology is relatively neglected by surgeons in the UK and no papers were presented from this country. This probably related to poor advertisement of the Florida meetings on our side of the Atlantic.

The book presents good, up-to-date, critical reviews of many aspects of wound healing. For those interested there is a wealth of current literature and many references presented Chapters which in my opinion present the most interesting topics include those covering aetiology and identification of the huge resources poured into chronic wound care. Little reference is made to UK work in the field. There are good chapters looking at the biology and clinical use of growth factors which indicate the work that is yet to come. The established use of cultured allografts (where 1 cm^2 of donor skin can be cultured to cover total body surface) and the scarless healing of fetal repair are well covered, with methods of measurement in wound healing, dressings and exploration of the content of wound fluid. The potential for enhancing wound healing when it is progressing optimally is still unclear

The text is presented as direct reproduction, avoiding the time (and expense) of proofreading in house by the publishers. The index and contributor list are typeset and I wish the rest of the book was also, as the text is not easy to read. The book is described as vital reading: it is, but only to those who have an established interest. I am unaware of its UK price.

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Notices and announcements

27–29 May 1992
European Council for Coloproctology Fourth Biennial Congress
Marseille, France
Information. Patricia Vallet, Alice Congrès, 12 Cours Jean Ballard, BP 2028 13201 Marseille cedex 01, France

2–5 June 1992
Eurochirurgie '92 2nd European Congress of Surgery
Brussels, Belgium
Information: Congress Secretariat: Eurosurgery '92, Brussels International Trade Fair, Place de Belgique, B-1020 Brussels, Belgium

3 June 1992
Surgical Problems in Early Breast Cancer
Solihull, UK
Information Mrs V Hall, British Association of Surgical Oncology, Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

5 June 1992
Logistic Regression and Survival Analysis
Limburg, The Netherlands
Information Annie Simon, Faculty of Health Sciences, University of Limburg, PO Box 616, 6200 MD Maastricht, The Netherlands

7–10 June 1992
International Congress on Cancer of the Esophagus
Genoa, Italy
Information: Secretariat, Luigina Bonelli, Unit of Clinical Epidemiology and Trials, Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

7–11 June 1992
4th World Congress of Hepato-Pancreato-Biliary Surgery
Hong Kong
Information Secretariat, International Conference Consultants Ltd , Suits A and B, 16/F., Casey Building, 38 Lok Ku Rd, Sheung Wan, Hong Kong

24–27 June 1992
The Endocrine Society 74th Annual Meeting
San Antonio, Texas, USA
Information Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

28 June–3 July 1992
4th Oxbridge Organ Transplantation Course
Cambridge, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

29 June–3 July 1992
Practical Nutritional Support – Third Annual Training Course for Clinicians
Southampton, UK
Information Mr Brendan Moran, Department of Human Nutrition, University of Southampton, Southampton SO9 3TU, UK

2–3 July 1992
Surgical Research Society Meeting
Edinburgh, UK
Information: Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

5–10 July 1992
Immunology and the Nervous System: Clinical Aspects
Oxford, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

10–11 July 1992
Hong Kong Surgical Forum – Summer 1992
Hong Kong
Information Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

10–12 July 1992
Minimally Invasive Medicine – From Diagnosis to Therapy
Berlin, Germany
Information KIT Marketing Services GmbH, Behrenstraße 23, 0-1080 Berlin-Mitte, Germany

13–17 July 1992
Annual Diagnostic Imaging Seminar
Martha's Vineyard Island, Massachusetts, USA
Information: Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, USA

16–18 July 1992
XVIIth International Update on Liver Disease
London, UK
Information Professor Neil McIntyre, University Department of Medicine, Royal Free Hospital, London NW3 2QG, UK

22–24 July 1992
British Association of Paediatric Surgeons XXXIX Annual International Congress
Leeds, UK
Information Secretariat (BAPS), Bell Howe Conferences, 1 Willoughby Street, Beeston, Nottingham NG9 2LT, UK

2–4 September 1992
Ultrasound Angiography '92
Southampton, UK
Information Secretariat, Ultrasound Angiography '92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK

9–11 September 1992
2nd Nottingham International Breast Cancer Meeting
Nottingham, UK
Information Mrs Wendy Bartlam, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

20–23 September 1992
VIIth Edmondo Malan International Day of Surgery – Endo-laparoscopic and Mini-invasive Surgery
Parma, Italy
Information Professor Gian Carlo Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43100 Parma, Italy

20–24 September 1992
Combined Meeting of the Association of Surgeons of Great Britain and Ireland and Trinity College Dublin Quatercentenary Meeting
Dublin, Ireland
Information Mr T N Walsh, Department of Surgery, St James's Hospital, Dublin, Ireland

24–26 September 1992
Postgraduate Course – Principles of Colon and Rectal Surgery
Minnesota, Minneapolis, USA
Information. Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue Southeast, Minneapolis, Minnesota 55414, USA

7–8 October 1992
VIIth National Conference of the Association of Paediatric Surgeons of Pakistan
Lahore, Pakistan
Information Dr Z. B Attar, Department of Paediatric Surgery, National Institute of Child Health, Karachi, Pakistan

27 October–4 November 1992
Anaesthesia and Surgical Intensive Care: Controversies and Conflicts
Bristol, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

2–6 November 1992
Specialist Short Courses: Advanced Surgical Techniques
London, UK
Information Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

6–7 November 1992
International College of Surgeons 38th Annual Meeting of the Japan Section – 'Controversies in Surgery'
Tokyo, Japan
Information Professor K Kimura, Department of Surgery, Tokyo Medical College, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan 160

15–18 November 1992
Update and Future Trends in Fibrin Sealing in Surgical and Non-surgical Fields
Vienna, Austria
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